THE

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1. Davidson, C.S., et al.: Sodium-Restricted Diets, Publication 325, Division of Biology and Agriculture, National Research Council, July 1954, pp. 40, 44.
2. Penna, R.P., et al. (eds.): Handbook of Nonprescription Drugs, Washington, D.C., American Pharm. Assn., Ed. 5, 1977, pp. 13-17.
3. Penna, R.P.: Antacids, in Handbook of Nonprescription Drugs, Washington, D.C., American Pharm. Assn., 1973 Ed., pp. 12, 14.
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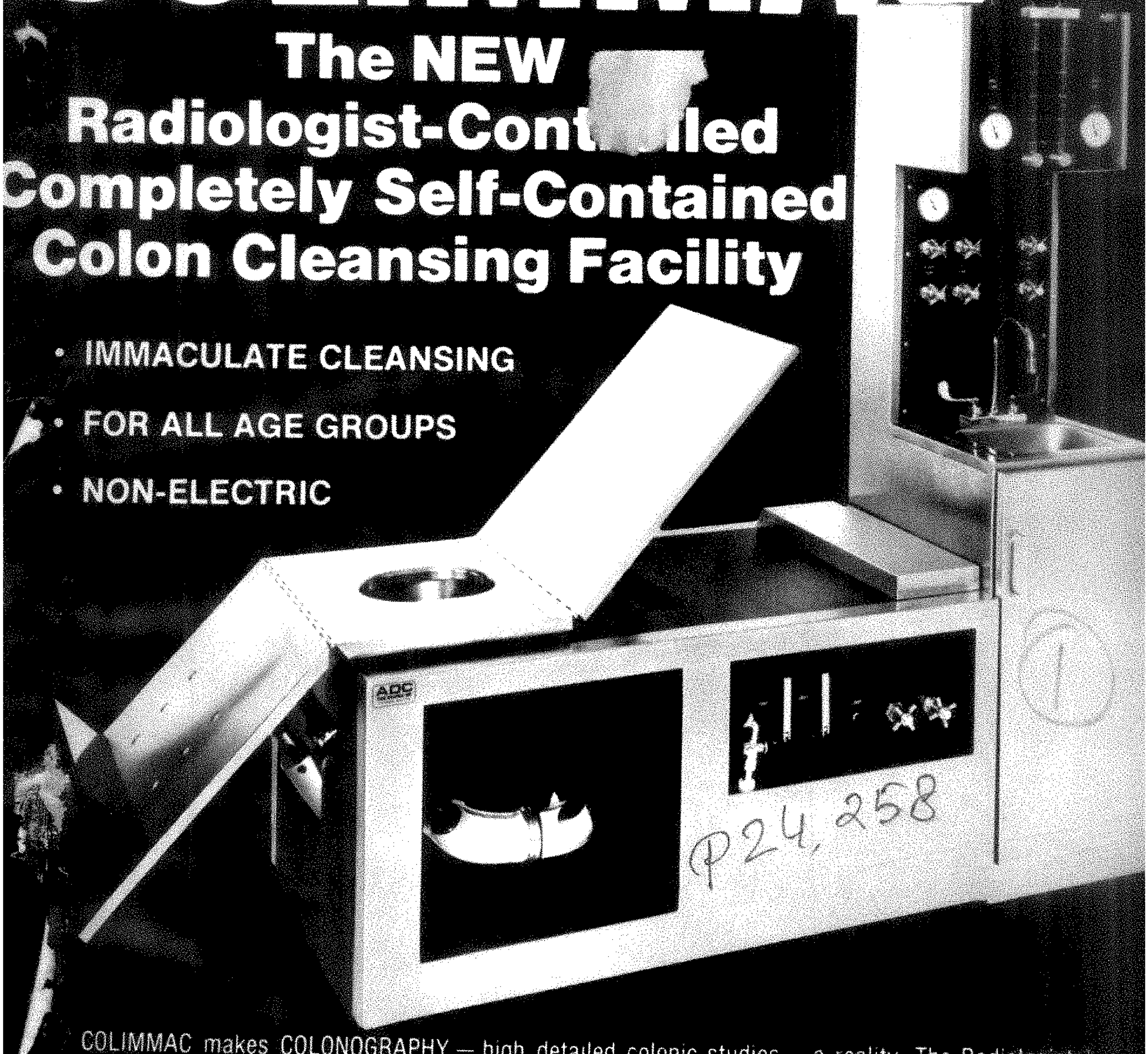

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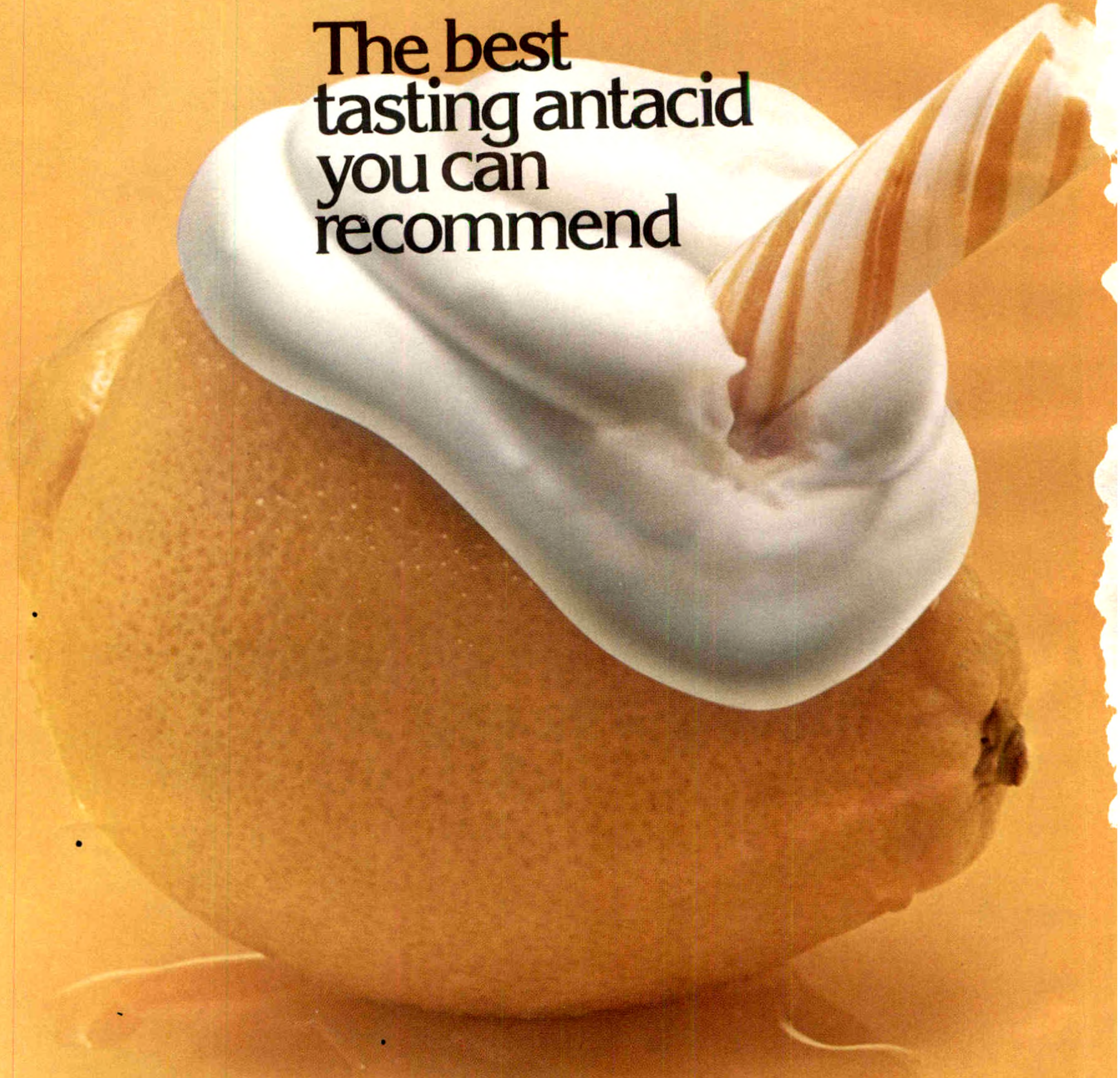

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THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Clinical Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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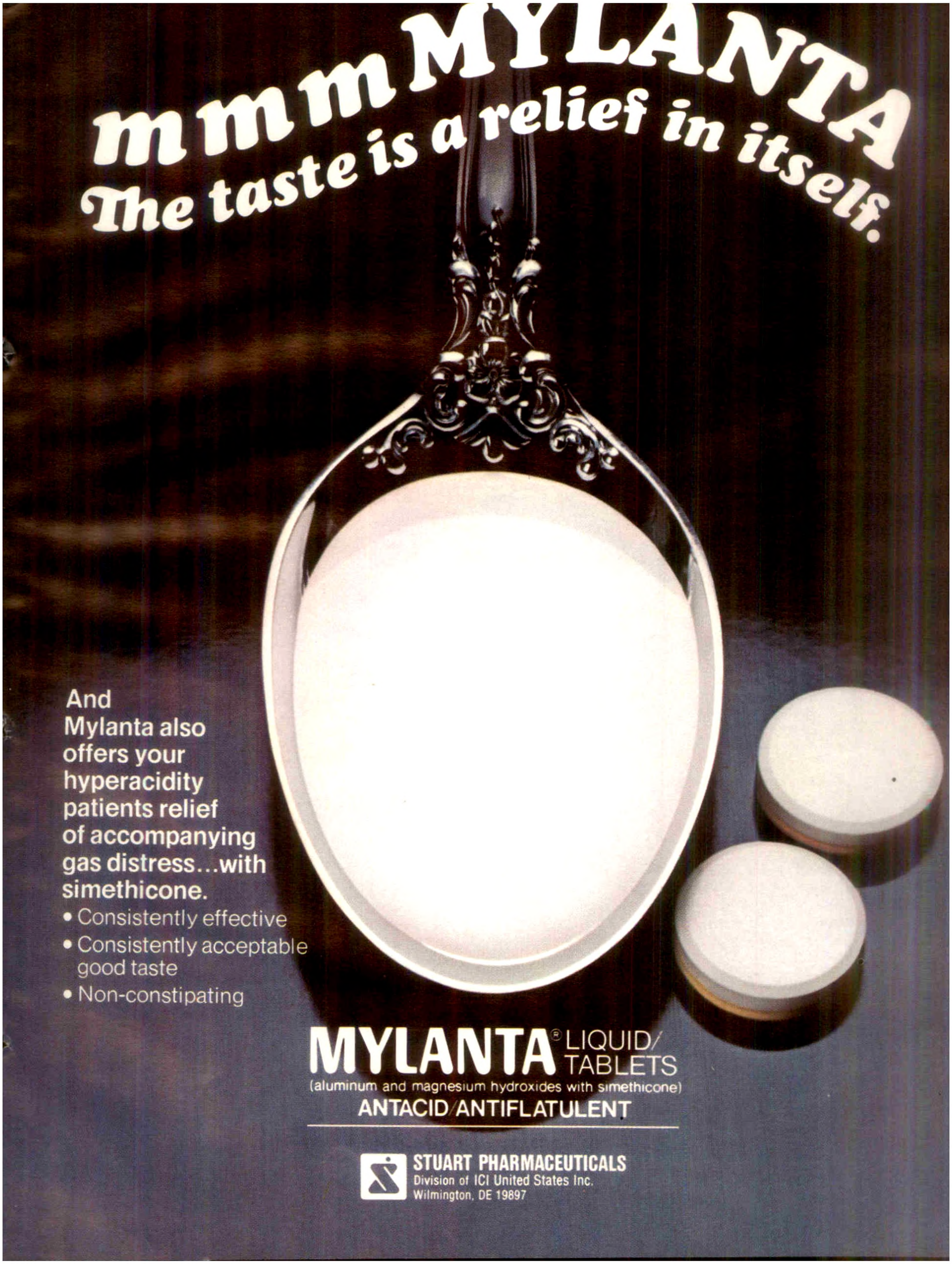

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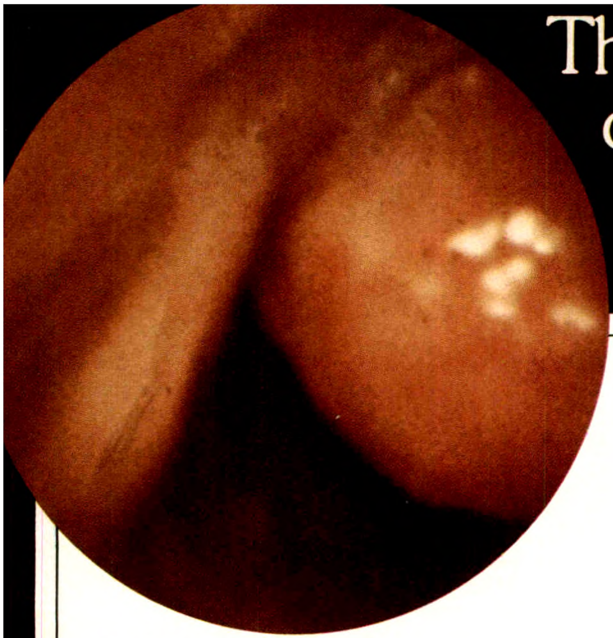

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Fulminant Hepatic Failure

Annotated Abstracts of a
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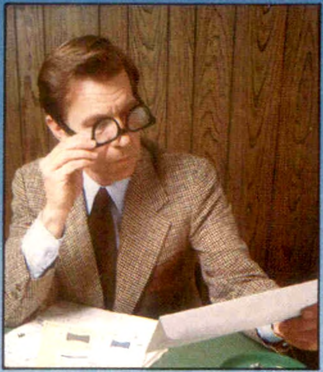
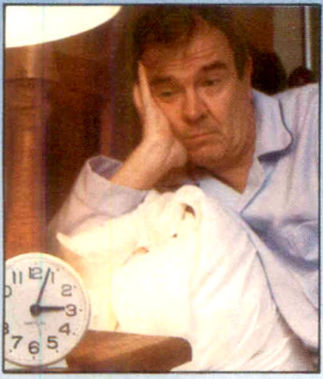
* * *

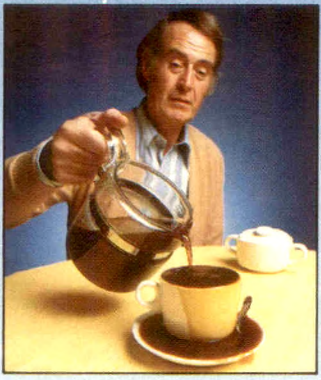
Co-sponsored by the National Institute of Arthritis, Metabolism and Digestive Diseases and the John E. Fogarty International Center for Advanced Study in the Health Sciences.

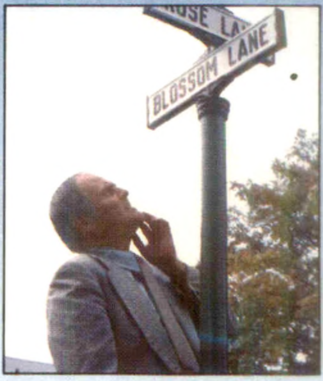
Which of these cirrhotic patients has portal-systemic encephalopathy (PSE)?

(Also called Hepatic Encephalopathy, Hepatic Coma.)









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Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, The Marriott, Denver, Colo., 28-30 September 1978.

Postgraduate Course of the American Gastroenterological Association, MGM Grand Hotel, Las Vegas, Nev., 20, 21 May 1978.

79th Annual Meeting of the American Gastroenterological Association, MGM Grand Hotel, Las Vegas, Nev., 22-25 May 1978.

Endoscopic Interpretation, Postgraduate Course of the American Society for Gastrointestinal Endoscopy, MGM Grand Hotel, Las Vegas, Nev. 25, 26 May 1978.

6th World Congress of Gastroenterology, Madrid, Spain, 5-9 June 1978.

Selected Disorders of the Colon, Postgraduate Seminar co-sponsored by the American College of Gastroenterology, the Southern Medical Association and the University of Miami School of Medicine. Bahia Mar Hotel, Ft. Lauderdale Beach, Fla., 1-3 July 1978.

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(lactulose) Syrup

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose diet.

WARNINGS: *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

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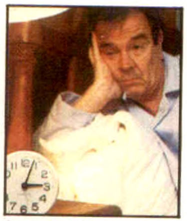
They all do!

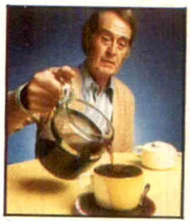
Case 1. 53-year-old retired submariner with cirrhosis of uncertain etiology and portacaval shunt

Case 2. 57-year-old widow with primary biliary cirrhosis



Case 3. 50-year-old male with alcoholic cirrhosis

Case 4. 43-year-old salesman with clinically stable Laennec's cirrhosis



Case 5. 55-year-old male with histologically proven cirrhosis

Case 6. 50-year-old male with Laennec's cirrhosis and portacaval shunt

Professional models were used to ensure patient privacy.

Suspect portal-systemic encephalopathy (PSE) in every patient with cirrhosis

Common early symptoms of PSE are:

irritability, euphoria, lack of concern for others, inappropriate behavior, faraway look, inversion of sleep pattern.

Results of recent investigations of PSE:

- Two-thirds of cirrhotic patients with portal hypertension without clinical evidence of PSE revealed impairment of cerebral function on psychometric testing. This dysfunction was in the same range as in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

These inapparent and early stages can last for hours, days, weeks, months or even years. Untreated, they lead to COMA. You can't depend on routine observation to detect PSE.

- Test every cirrhotic for PSE.
- Treat every PSE, regardless of stage.
- Remember, the early stages are the most common; the coma stage is only the tip of the PSE iceberg.

Cephulac (lactulose) Syrup effectively reverses acute and chronic recurrent PSE in over 75% of episodes, without serious adverse reactions, when used as directed.

- lowers blood ammonia levels
- improves mental state
- lessens EEG abnormalities
- permits more normal dietary protein intake
- makes it easier to treat the patient

References:

1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.

2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non-cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.

3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: Detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 72:1119, 1977.

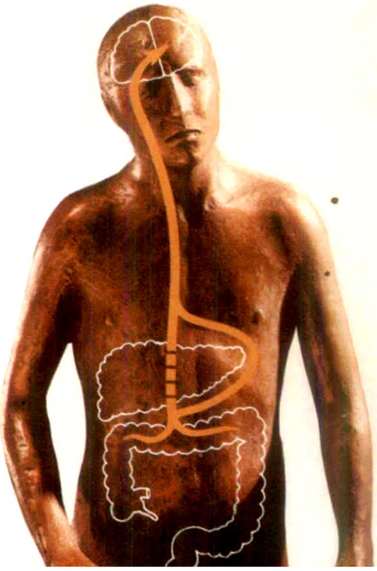
See adjacent page for prescribing information.

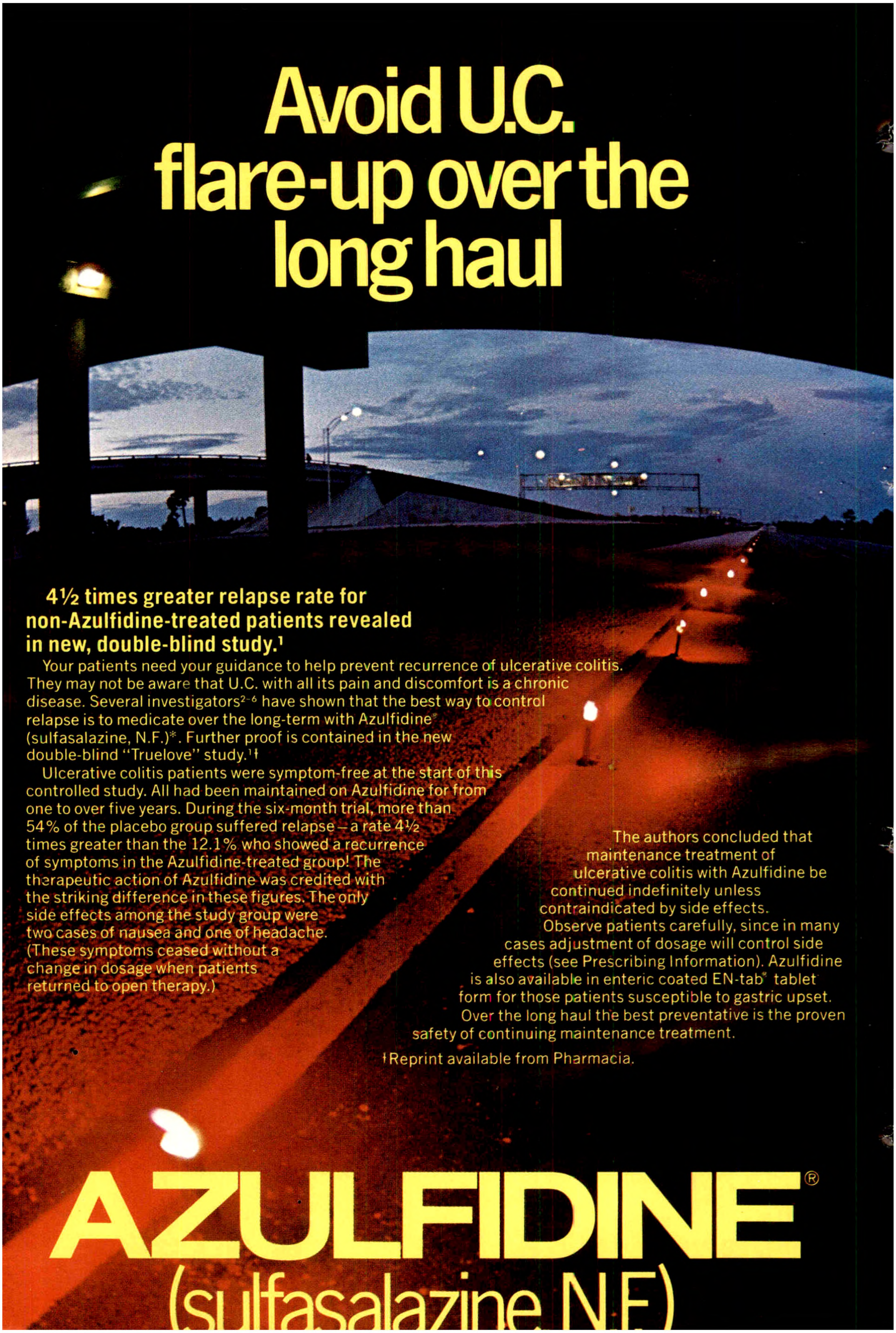
Cephulac®

(lactulose) Syrup

for the prevention and treatment of portal-systemic encephalopathy

(Also called Hepatic Encephalopathy, Hepatic Coma.)





4½ times greater relapse rate for non-Azulfidine-treated patients revealed in new, double-blind study.[1]

Your patients need your guidance to help prevent recurrence of ulcerative colitis. They may not be aware that U.C. with all its pain and discomfort is a chronic disease. Several investigators[2-6] have shown that the best way to control relapse is to medicate over the long-term with Azulfidine® (sulfasalazine, N.F.)*. Further proof is contained in the new double-blind "Truelove" study.[1†]

Ulcerative colitis patients were symptom-free at the start of this controlled study. All had been maintained on Azulfidine for from one to over five years. During the six-month trial, more than 54% of the placebo group suffered relapse—a rate 4½ times greater than the 12.1% who showed a recurrence of symptoms in the Azulfidine-treated group! The therapeutic action of Azulfidine was credited with the striking difference in these figures. The only side effects among the study group were two cases of nausea and one of headache. (These symptoms ceased without a change in dosage when patients returned to open therapy.)

The authors concluded that maintenance treatment of ulcerative colitis with Azulfidine be continued indefinitely unless contraindicated by side effects.

Observe patients carefully, since in many cases adjustment of dosage will control side effects (see Prescribing Information). Azulfidine is also available in enteric coated EN-tab® tablet form for those patients susceptible to gastric upset.

Over the long haul the best preventative is the proven safety of continuing maintenance treatment.

†Reprint available from Pharmacia.

AZULFIDINE®
(sulfasalazine, N.F.)
Tablets and EN-tabs®

INDICATIONS: AZULFIDINE (sulfasalazine, N.F.) is indicated in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis. AZULFIDINE EN-tabs are particularly indicated in patients who experience gastrointestinal intolerance after the first few doses of the drug, when such intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites and in those for whom a reduction in dosage does not alleviate the gastrointestinal effects.
CONTRAINDICATIONS: Hypersensitivity to sulfonamides or salicylates. In infants under 2 years. Intestinal and urinary obstruction. Pregnancy at term and during the nursing period. In patients with porphyria.
WARNINGS: The safe use of sulfonamides in pregnancy has not been established. Evaluate benefit to risk carefully when giving sulfonamides during pregnancy, especially at term, since kernicterus may be produced in the newborn. The teratogenic potential of most sulfonamides has not been thoroughly investigated in any species and a significant increase of cleft palate and other bony abnormalities has been observed when certain sulfonamides were given orally to pregnant rats and mice at 7 to 25 times the human therapeutic dose.

Deaths associated with the administration of AZULFIDINE (sulfasalazine, N.F.) have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and CNS changes and fibrosing alveolitis.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders.

Complete blood counts as well as urinalysis with microscopic examination should be done frequently.
PRECAUTIONS: Administer with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia.

Maintain adequate fluid intake to prevent crystalluria and stone formation.
ADVERSE REACTIONS: Adverse reactions have been observed in 5 to 55% of patients included in clinical studies reported in the literature. Experience suggests that with daily dosages of 4 g or more, adverse reactions tend to increase. The most common adverse reactions associated with AZULFIDINE therapy are anorexia, nausea, vomiting, and gastric distress. The following adverse reactions have been reported to occur during therapy with AZULFIDINE.

Blood dyscrasias: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, Heinz Body anemia, purpura, hypoprothrombinemia, "cyanosis," and methemoglobinemia.

Hypersensitivity reactions: Generalized skin eruptions, erythema multiforme (Stevens-Johnson syndrome), parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, pruritus, urticaria, photosensitization, anaphylaxis, serum sickness syndrome, chills, drug fever, periorbital edema, conjunctival and scleral injection, arthralgia, transient pulmonary changes with eosinophilia and decreased pulmonary function, allergic myocarditis, polyarteritis nodosa, and L.E. phenomenon.

Gastrointestinal reactions: Anorexia, nausea, emesis, abdominal pains, diarrhea, impaired folic acid and digoxin absorption, stomatitis, pancreatitis, and hepatitis.

CNS reactions: Headache, vertigo, tinnitus, hearing loss, peripheral neuropathy, transient lesions of posterior spinal column, transverse myelitis, ataxia, convulsions, insomnia, mental depression, hallucinations and drowsiness.

Renal reactions: Crystalluria, hematuria, proteinuria, and nephrotic syndrome. Toxic nephrosis with oliguria and anuria.

Incidents of alopecia and reduction in sperm count and viability have also been reported.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross sensitivity may exist with these agents.

AZULFIDINE (sulfasalazine, N.F.) produces an orange-yellow color when the urine is alkaline. Similar discoloration of the skin has also been reported.
SUPPLIED: Tablets and EN-tabs (enteric-coated) 0.5 gm. in bottles of 100 and 500. Also available as Azulfidine Unit Dose in boxes of 100's and 1000's.
IMPORTANT: See full prescribing information before administering AZULFIDINE.

References:
1. Dissanayake, A.S. and Truelove, S.C.: Gut 14:923-926, Dec. 1973.
2. Bargen, J.A.: Amer. Surg. 28:630-637, Sept. 1962.
3. Hightower, N.C., Jr., et al: Amer. J. Digest. Dis. 3:722-733, 861-876, 931-941, Oct., Nov., Dec. 1958.
4. Roth, J.L.A.: Chapter 69, in Bockus, H. (ed.): Gastroenterology, Vol. II, W.B. Saunders Company.
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6. Goldstein, F. and Thornton, J.J.: Consultant 14:96-103, July 1974.

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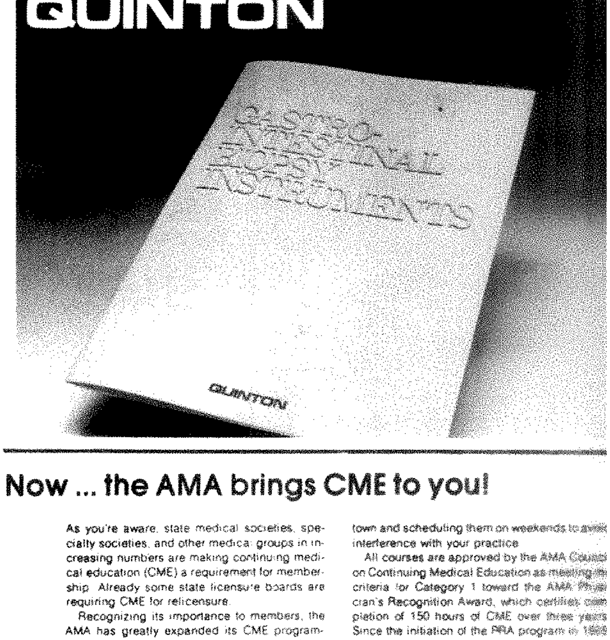

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in irritable colon*

When stress makes waves for the spasm reactor...

A normal reaction to emotional stress is a marked increase in both the strength and frequency of wave-like contractions of colonic motility.[1] However, in the patient with irritable bowel syndrome, this psychovisceral reaction is of greater intensity and duration than normal.[2]

The result can be G.I. spasm.

When spasm and pain associated with irritable bowel syndrome call for treatment beyond your counseling and reassurance, Donnatal may prove to be a helpful adjunct. The smooth central sedation and prompt peripheral antispasmodic/anticholinergic action of Donnatal may provide this symptomatic relief necessary to help calm the waves …and quell the spasm.

References: 1. Almy, T.P., Kern, F., and Tulin, M.: Alterations in colonic function in man under stress. II: Experimental production of sigmoid spasm in healthy persons. *Gastroenterology* 12(3):425-436, 1949. **2.** Almy, T.P., Hinkle, L.E., Berle, B., et al.: Alterations in colonic function in man under stress. III: Experimental production of sigmoid spasm in patients with spastic constipation. *Gastroenterology* 12(3):437-449, 1949.

*Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

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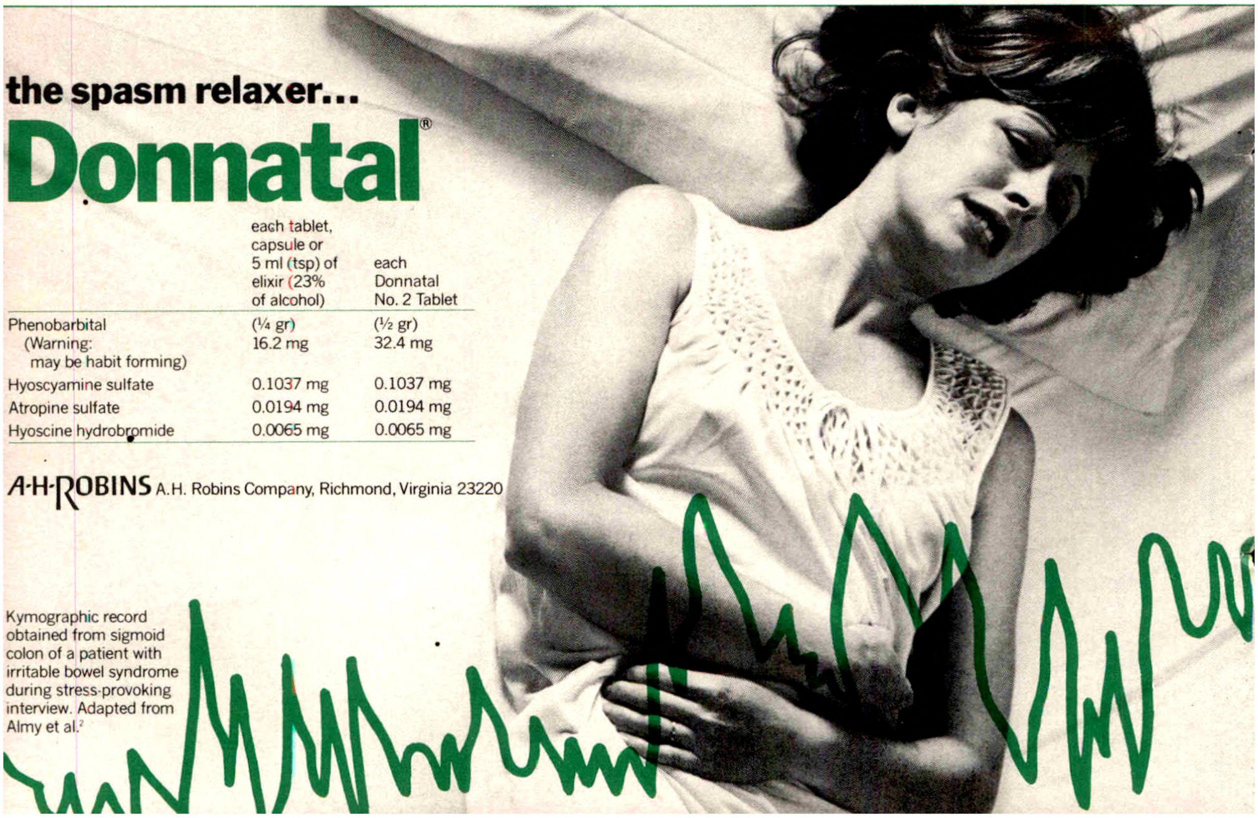

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Hyoscine hydrobromide	0.0065 mg	0.0065 mg

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Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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THE American Journal OF Gastroenterology

A monthly journal of Clinical Gastroenterology, Proctology and Allied Subjects
FORMERLY THE REVIEW OF GASTROENTEROLOGY

VOLUME 69 FEBRUARY, 1978 NUMBER 2

PRESIDENTIAL ADDRESS*

F. WARREN NUGENT, M.D., F.A.C.G.
Boston, MA

Gastroenterology is currently faced with a variety of problems. Some of these are being solved but unfortunately others of serious nature have yet to be settled. In recent years there has been a clarification of the impact of digestive diseases on the health and economy of the nation. Two national conferences have been held which have emphasized the dimensions of the problem. At the present time, a congressional commission on digestive diseases is carrying out further studies and attempting to address the issues and make suitable recommendations. How best to educate physicians, the public and the congress regarding digestive diseases? What are the best methods of training in clinical and in research areas and where should the balance be struck? How do we best deliver care for these diseases while at the same time deliver them at reasonable cost?

The effect of gastrointestinal disease on our society is profound—for example, 18 million people suffer from digestive diseases in one form or another. Approximately 20% of all hospital admissions are for these maladies, the number one cause of hospitalization in the United States. Excluding tonsilectomy, one-third of all operations are performed for the treatment of digestive diseases. Except for the common cold, digestive diseases are the basis for more days lost from work than any other single cause, resulting in serious economic loss to our country. Two of the more common problems in the gastrointestinal tract, peptic ulcer and gallstones, each cost the country approximately three billion dollars yearly in direct costs and lost productive work.

During this same period in which the impact of digestive diseases was being better defined, there have been great advances in our knowledge as a result of accelerated clinical and basic research studies. Technological advances have come about in a parallel fashion and with fiberoptics we have now literally opened a window into the inside of the patient.

We are gratified that there has been great progress in the diagnosis and treatment of digestive diseases. Alarming, however, is the knowledge that the cost has skyrocketed and although there has been impressive improvement in the quality of life for many patients suffering from these diseases, there has been no proven increase in longevity. This has led to disappointment and frustration on the part of the public and the congress. The slumbering giant of government has awakened and is about to give forth a mighty roar of legislation, much of which may restrict the freedom of the physician to practice in the traditional American way. Regulation of medical school admission, distribution of physicians, geographically and by specialty, control of hospital beds and costs, regulation of drugs and when and how they may be prescribed, regulation of medical laboratories and even physicians' offices, are but a few of the areas in which the government is now formulating legislation.

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* Delivered at the 42nd Annual Convention of the American College of Gastroenterology, New Orleans, La., 24, 25, 26 October 1977.

We, the practicing physicians, have the opportunity and the responsibility of influencing these changing patterns in medical practice to as great an extent as possible. We must make every effort to ensure that the practice of medicine continues to deliver the best possible care to our patients. It will be sad if our legacy is a form of practice encumbered by governmental regulations and lacking in the excitement and intellectual stimulation that we have all enjoyed. If so, it will inevitably be accompanied by a deterioration of medical care.

The potential for input on our part is great. As, however, Linus from the Peanuts comic strip commented "there is no heavier burden than a great potential". We must try to fulfill this potential.

How can this be done? Let us start with the individual actions of physicians. Whether justified or not, health care is now considered by most of the people to be a right. Although public satisfaction with physicians is approximately 90% favorable according to the latest Gallup poll, there are areas of dissatisfaction. It is felt that physicians have a condescending attitude towards their patients, keep them waiting too long, are insensitive to personal dignities and do not adequately explain the nature of the patient's problem. There is some resentment regarding the status and the income of physicians. Our historical allies, such as business, are leaving us and at this time our strongest supporters are the blue collar workers. On the other hand, the segment of society most critical of the medical profession is the highly educated group. It is obvious that we must mend our fences in some of these areas if we wish to continue to have the support of the public in the battles that lie ahead of us.

We must support the national organizations that represent us. The largest and most powerful of these is the American Medical Association. A great deal of criticism has been leveled at this organization in recent years. Despite the fact that we may not agree with all positions taken by the American Medical Association, it is the voice of medicine in a sense that no other organization is. The American College of Gastroenterology is represented in the American Medical Association both on the Section Council on Gastroenterology and on the Interspecialty Advisory Board. I have had the opportunity of serving in some of these areas and seeing first hand the aims and efforts of the American Medical Association. Let me assure you that they have our best interests at heart and are putting forth a massive effort to influence the national health insurance legislation that is now considered an inevitability. This is equally true in regard to many other actions under study by the Department of Health, Education and Welfare.

Last, but of course not least, are the specialty societies. Here again, we have the opportunity of playing a major role in the settlement of many issues that are close to our heart. How many gastroenterologists should there be? Where should they practice? Should they be allowed to do primary medicine as well as secondary and tertiary care? How should they be paid and who should set the fees? Government agencies will attempt to settle these questions for the most part and it is up to us to exert as much influence as possible on these agencies. As the major organization representing clinical gastroenterology we, the American College of Gastroenterology, must make every effort to insure that the clinician is adequately represented in these councils. Funding agencies must realize that a proper balance should be struck between clinical training and research training. In the recent past, emphasis has been on research training, even when much of the time spent by the trainee is actually in the clinical area. The American College of Gastroenterology now has a major voice in all of the councils involved with the digestive diseases. We are well represented in the principal lay organizations such as the American Digestive Disease Society and the National Foundation for Ileitis and Colitis. We are represented in the American Medical Association and on the Congressional Commission on Digestive Diseases. We have an equal voice along with the American Gastroenterological Association, the American Association for the Study of Liver Disease, the American Society for Gastrointestinal Endoscopy and the Society for the Surgery of the Alimentary Tract in the newly formed Federation of Digestive Disease Societies which hopefully will serve as an umbrella over the digestive disease organizations. In the past, our specialty has been fragmented but now we hope to speak with one voice. I feel certain that this one voice will be more clearly heard than were the often contentious voices of the individual societies.

The American College of Gastroenterology has grown in the past few years, in size, in strength and in political influence. We must exercise this influence in the name of clinical gastroenterology. We must develop strong leaders who will insure that our voice is heard and that we are adequately represented in the national arena.

In short, we must work together to improve our services to our patients. The rewarding by-product of this service will be an inner strength in our specialty, of greater proportions than ever before.

In closing let me express my sincere appreciation for the honor and privilege of serving as your president for the past year. I would like to thank all of the officers and members who have given their time and effort to help solve the problems we have faced during the past year.

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Communication from Abroad

Intraluminal Pressure Profiles and Mucosal Movements in the Stomach and Duodenum

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J. C. VERMAAK, M.B. Ch.B., M.Med.†
and
J. MOUTON, B.Sc.†
Tygerberg, South Africa

Records of a possible relationship between intraluminal pressure profiles and movements of the mucosal layer are not obtainable. A prospective study was initiated to investigate this aspect in the pyloric region of the stomach and in the duodenum. The results indicate that simultaneously with certain contraction waves of the walls, all mucosal folds within the confines of the contraction change in direction to become longitudinal, thus forming longitudinal intraluminal mucosal troughs. (It is presumed that these will enhance linear flow of semiliquid intestinal contents.) The phenomenon occurs regularly and is an inherent component of various contraction waves, including peristalsis. The definition of peristalsis should probably be expanded to include reference to this mucosal component. These normal findings may serve as a base line for the investigation of mucosal motility patterns in pathological situations, e.g. peptic ulcer.

INTRODUCTION

Seeing that the gastrointestinal mucosa is in intimate mechanical contact with swallowed substances or the products of digestion, it comes as some surprise to learn that a consideration of any possible participation of the mucosa in intestinal motility has been almost universally omitted. In gastrointestinal pressure studies possible movements of the mucosa are hardly ever mentioned.[1] In physiology a search for meaningful information is usually nonrewarding.[1] In anatomy and related disciplines it appears to be accepted that mucosal folds are of little consequence, except for the fact that they are reputed to have a characteristic position in specific segments of the gastrointestinal tract.[1] It is usually stated or implied that they are stationary.[1] The fundamental observations of Forssell,[2,3] as confirmed by Brooks, et al,[4] are largely ignored. Only in radiology have fold movements been described in a number of isolated observations. These have been enumerated elsewhere and at the same time an attempt was made, on radiological evidence, to propound a general concept of mucosal fold movements.[1]

The purely visual evidence supplied by radiology is probably inadequate for the postulation of firm conclusions. Consequently pressure studies combined with radiological imaging were instituted to investigate the problem. It was felt that such studies may aid in the clarification of certain aspects of gastrointestinal motility,

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* Department of Radiology, University of Stellenbosch and Tygerberg Hospital.
† Department of Internal Medicine, University of Stellenbosch and Tygerberg Hospital.

especially in view of the description of various intrinsic intestinal reflexes.[5,6]

MATERIALS AND METHODS

Intraluminal pressure recordings by means of an air-filled system and a miniature balloon were obtained in the pyloric region of the stomach in five subjects and in the second or third parts of the duodenum in six other subjects. A pressure sensitive system usually used for cardiovascular physiology, with some modifications, was employed. It consisted of a monitor (Statham SP1400) (Statham Instruments Inc., Los Angeles), a miniature transducer (Statham P37B), a recorder (Statham SP2006) and a catheter, 125 cm. in length with an outside diameter of 2 mm. A miniature balloon 38 mm. in length and 8 mm. in diameter, covered the six endholes of the catheter. The volume of air introduced into the balloon to achieve zero pressure was 0.8 ml.

All subjects were volunteer adult ambulatory out-patients with vague abdominal symptoms. In none could an organic lesion be demonstrated with an upper gastrointestinal barium meal series. After an overnight fast the balloon was manipulated into position under TV screening with the subject erect. Four mouthfuls of barium sulfate suspension were swallowed for purposes of localization and in order to demonstrate the mucosal folds. In the absence of motor activity the diameter of the pyloric region was approximately eight times the diameter of the balloon (visible because of its air content) and the diameter of the duodenum three times that of the balloon.

Artifacts such as subject movement, coughing and pressure increases produced by the radiographic apparatus were identified and excluded. Peak pressure increases were correlated with motility as filmed radiographically and vice versa.

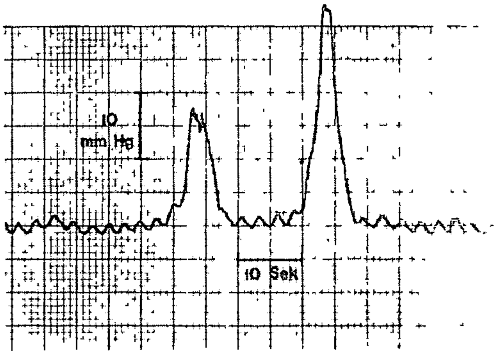

Fig. 1—Pyloric region, showing two Type I waves. With both waves mucosal folds changed in direction to become longitudinal. Base line indicates intraluminal pressure in absence of radiologically visible motor activity. 10-second marker on base line.

RESULTS

In the stomach the measuring balloon was placed on the immediate oral side of the pyloric orifice, i.e. in the *canalis egestorius* as defined by Forssell[7] and Torgersen.[8] The base line represented the intraluminal pressure in the absence of radiologically visible motor activity. At this stage the mucosal folds were seen to be circular and oblique in direction.

The following two distinct waves of pressure increase were noted: 1. Irregularly occurring, nonrhythmic contractions causing intraluminal pressure increases varying from 9-34 mm. Hg. (the majority being in the range of 12-25 mm Hg). These waves lasted from 5-21 seconds, the majority being in the 6-10 second range (Fig. 1). They occurred repeatedly in all subjects and conform to Type I contractions.[9,10]

Simultaneous radiological TV recording showed that these waves conformed to the contractions described as "antral systole"[11] or contraction of the *canalis egestorius*.[7,8] The details of these contractions, as seen radiographically, have been described on the basis of the underlying comparative anatomy of the part.[12] The terminal antral contraction (TAC) occurring in dogs and described by later authors[13] can, in our opinion, be explained on this basis. Torgersen showed that the muscular build and movements of the *pars pylorica* of the canine stomach are identical to those of the human.[8] Carlson, et al did not refer to these fundamental anatomical findings. They did show that TAC produced a sharp rise in intraluminal pressure.[13]

During these waves the direction of the mucosal folds changed from circular and oblique to longitudinal. The higher the pressure wave recorded, the more intense the contraction appeared to be radiologically. At its peak all folds within the contracted area had changed to longitudinal. 2. In two of the subjects compound waves, consisting of a rise in base line pressure of 3-5 mm. Hg. and lasting for 10-40 seconds, on which were superimposed waves of shorter duration (3-5 seconds) and higher amplitude (up to 12 mm. Hg.), were seen. These conform to Type III waves.[10] The change in the direction of the mucosal folds was identical to that occurring in Type II waves.

In the second and third parts of the duodenum the base line again represented the intraluminal pressure in the absence of radiologically visible motor activity of the walls. At this stage the majority of mucosal folds were either circular or oblique. At times a more complex, branching pattern with polyhedral figures was seen.[14] The following two waves of pressure increase were noted: 1. Nonrhythmic, simple, brief monophasic waves, causing an intraluminal pressure increase of 4-35 mm. Hg. (the majority being in the 7-34 mm. Hg. range) and lasting for 2-8 seconds (Fig. 2). They occurred repeatedly in all subjects and conform to Type I duodenal waves.[15-17] It was suggested that these should be designated phasic waves.[18] These waves were clearly visible radiologically and with each wave all mucosal folds within the area of contraction changed to longitudinal. 2. In two of the subjects nonrhythmic, complex waves consisting of a rise in base line pressure of 3-4 mm. Hg. and lasting from 40 seconds to 2½ minutes, with superadded peaks of 19-23 mm. Hg. and lasting for 5-6 seconds, were seen occasionally. These conform to Type III waves.[15-17] It was suggested that these should be designated tonic waves.[18] During the peak pressure increases all mucosal folds changed in direction to become longitudinal.

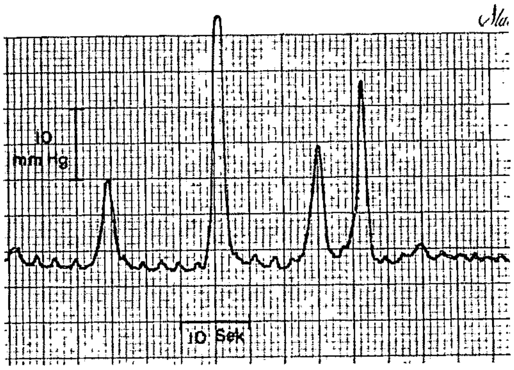

Fig. 2—Four monophasic duodenal waves. During all four waves mucosal folds changed in direction to become longitudinal.

COMMENT

Intraluminal pressure measurements show that during Type II and Type III contractions in the pyloric area (*canalis egestorius*, "terminal antrum") and during Type I (phasic) and Type III (tonic) contractions in the duodenum, all mucosal folds within the contracted area changed in direction to become longitudinal. During the height of the contraction only longitudinal folds were present in the contracted areas. Thus it can be concluded that the mucosal folds are not static, as so often stated and that mucosal movements participate in and constitute an inherent component of the contraction waves

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mentioned. Seeing that mucosal troughs exist between adjacent mucosal folds, it is evident that longitudinal intraluminal mucosal troughs are formed by this mechanism concurrently with the contraction of the walls. While it has not been proved, it is assumed that the effect of this may be to enhance linear flow of semiliquid intestinal contents. This phenomenon no doubt constitutes one of the best examples of the "independent but co-ordinated movements" of the *muscularis externa* and the mucosa, orginally mentioned by Forssell.[2, 3]

The Type II pyloric waves ("antral systole", conforming to TAC waves in canines) are of a peristaltic or peristaltic-like nature, as are the Type I duodenal (phasic) waves. The definition of "peristalsis" remains elusive, except in the medical dictionaries, where the consensus appears to be that it is a wormlike movement of a tubular structure, consisting of alternate waves of relaxation and contraction in the walls, by which the contents are propelled.[19-21] In another definition relaxation is not mentioned specifically.[22] According to Horrobin[23] peristalsis is a contraction, preceded by relaxation, spreading down a long length of intestine, thus propagating the contents; it depends on an intrinsic intestinal reflex.

Bulbring, et al[24] appeared to be of the opinion that "peristalsis" should be limited to those movements which depend on the peristaltic reflex. This can be defined as an intrinsic intestinal reflex, mediated through a local neural pathway and initiated by an increase in intraluminal pressure (usually a bolus), in which co-ordinated contractions of both the longitudinal and circular layers of the wall occur, thus propelling the contents in a cephalocaudal direction. They stated that some workers failed to make a strict distinction between peristalsis and other intestinal contractions.

It is generally agreed that the term "peristalsis" is often used carelessly to indicate various forms of motor activity. Texter[25] pointed out that it has been used in an inexact fashion to indicate propulsion, thus contradicting the definitions mentioned above. For these and other reasons it is suggested that the definition of peristalsis should be considered anew. Very seldom, for instance, is any mention made of the underlying electrical activity and nowhere have we encountered reference to its mucosal component as described above in the *pars pylorica* and duodenum. The present findings show that characteristic mucosal movements occur in what are generally considered to be peristaltic or peristaltic-like as well as segmenting (mixing) movements in these areas. A close functional relationship between the mucosa and the *muscularis externa* has recently been described by Hukuhara and associates in different intrinsic intestinal reflexes.[5, 6] On stimulation of the exposed intestinal mucosa in anesthetized animals by a variety of means they observed contraction of the *muscularis externa* above and relaxation below the point of stimulation. This effect was shown to be due to an intrinsic intestinal mucosal reflex. On *in vivo* electrical stimulation of the serosa of the intact small bowel in the Cape baboon (*Papio ursinus ursinus*) we noted contraction of the *muscularis externa* with a simultaneous change in the direction of the mucosal folds from circular to longitudinal.[1]

Consistent and characteristic simultaneous movements of the *muscularis externa* and the mucosa have thus been demonstrated in normal subjects. The question of mucosal movements in the presence of disease remains unanswered. The converging mucosal folds of peptic ulcer are well known to endoscopists and radiologists. Does this imply a dissociation of movement between the mucosa and the *muscularis* *externa*? Are combined movements of the mucosa and *muscularis* affected by early gastric carcinoma? It is suggested that studies be instituted to find an answer to these and related problems.

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The Value of Gray Scale Ultrasound in the Differential Diagnosis of Surgical and Nonsurgical Jaundice

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INTRODUCTION

The problem of the icteric patient has challenged the diagnostic skills of physicians for many centuries. In the majority of instances, the physician, by eliciting a detailed history, carefully performing a physical examination and using a few laboratory tests is able to separate those patients requiring operation for the relief of mechanical obstruction of the biliary tree from those with medical or hepatocellular jaundice. Unfortunately, with a small percentage of patients, the diagnosis may be quite difficult. Those patients with jaundice of uncertain etiology require further evaluation in order to define whether obstruction is present and, if so, to determine the cause, the site and the course of action which should be followed. The evaluation of such patients is not standardized and a logical approach must be used to answer the important questions.

A variety of diagnostic procedures have been developed to directly or indirectly evaluate the anatomy of the liver and biliary passages. Traditional noninvasive radiographic technics, such as oral or intravenous cholangiography, are often of limited use because opacification of the biliary tree is usually impossible with a serum bilirubin of more than 3.5 mg.% and is unlikely with even modest elevations of the serum bilirubin.[1-4] Radionuclide scanning of the liver with Technetium or Rose Bengal can be used but this technic will rarely provide diagnostic information except in patients in whom large discrete filling defects are noted. If the situation warrants, other directly invasive procedures such as transhepatic cholangiography[5, 6] and endoscopic retrograde cholangiography are available.[7, 8] These procedures are frequently successful in defining the site of obstruction but should not be undertaken unless the physician is willing to proceed to operation since the complications of the procedures frequently require surgical intervention. Complications include ascending cholangitis occurring after the injection of contrast material behind an obstruction, bile peritonitis, and bleeding.

In some patients, direct operative intervention, either by a limited procedure such as the "mini-lap"[9] or by a formal exploratory laparotomy, may be required Recently, ultrasonography has been introduced as a diagnostic tool. Ultrasonography is an inexpensive, safe procedure that provides immediate information from which diagnostic and therapeutic decisions can be made. The purpose of this paper is to discuss the role of ultrasonography in the

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TABLE I

FINAL DIAGNOSIS IN PATIENTS WITH SUSPECTED OBSTRUCTIVE JAUNDICE

Diagnosis	No. of patients	
Cancer		
Pancreas	9	
Ampullary	1	
Gastric	2	
Hepatoma	2	
Cholangiocarcinoma	1	
Islet cell carcinoma	1	
Subtotal		16
Choledocholithiasis		6
Pancreatitis		5
Liver disease		
Alcoholic hepatitis	6	
Toxic hepatitis	1	
Sarcoidosis	1	
Subtotal		8
Total		35

evaluation of the patient with suspected obstructive jaundice.

MATERIALS AND METHODS

Thirty-five consecutive patients, 19 men and 16 women between the ages of 19 and 78 years (average age 51 years), were evaluated by the Gastroenterology and Ultrasonography services at the Ben Taub General Hospital. These patients had been referred to ultrasonography because of the suspicion of obstructive jaundice. The correct diagnosis was established in each case within two weeks of ultrasonography, by laparotomy (24 cases), liver biopsy (9 cases), and autopsy (2 cases). The final diagnoses in these patients were malignant disease (16 patients), choledocholithiasis (6 patients), pancreatitis (5 patients) and intrinsic liver disease (8 patients) (Table I).

Ultrasonography was performed using a Picker Gray Scale unit and was recorded on Polaroid film using a standard 2.25 M.Hz. 19 mm. width, long-focused transducer. Transverse and longitudinal sections in the region of the biliary tree and oblique scans along the line of the pancreas were performed. The scanning was done at one-half centimeter intervals.

In each case, an attempt was made to measure the diameter of the common bile duct, the intrahepatic ducts and the gallbladder. Additionally, an attempt was made to scan the *porta hepatis,* the pancreas, the portal vein, the inferior vena cava, the superior mesentary veins and the liver. The common bile duct was delineated in transverse and longitudinal sections and measurements of the caliber were obtained. The continuity of the intrahepatic ducts with the common bile duct was examined. The intrahepatic ducts were measured in the middle of the longitudinal section of the right lobe of the liver at the level of the right kidney. When dilated ducts were noted, an effort was made to identify the site and nature of the obstruction.

RESULTS

We found that, with only one exception, we could separate patients with mechanical obstructive jaundice from those with intrahepatic cholestasis by the finding of a common bile duct 14 mm. or greater in diameter and/or a multiple intrahepatic duct 4 mm. or greater in diameter. The finding of a greatly enlarged gallbladder was of help in many cases. The intrahepatic and/or extrahepatic ducts could be visualized and measured in 30 of the 35 cases. Of the ducts that were visualized, the common bile duct was seen in 23 instances, the intrahepatic ducts in 22 instances and both the common bile duct and the intrahepatic ducts were visualized in 15 instances. Of these 30 cases, nine had intrahepatic cholestasis and 21 had extrahepatic biliary obstruction.

TABLE II

RESULTS OF ULTRASONOGRAPHY IN PATIENTS WITH EXTRAHEPATIC BILIARY OBSTRUCTION AND DILATED BILE DUCTS

Dilated biliary duct	No. of patients	Observation on other ductal system (No. of patients)		
		Normal	Dilated	Not seen
Common (≧ 14 mm.)	12	0	8	4
Intrahepatic (≧ 4 mm.)	16	4	8	4

These observations were based on a total of 20 patients; 8 had both types of biliary ducts dilated.

In 20 of the 21 patients with extrahepatic biliary obstruction, ultrasonography revealed dilated biliary ducts and the results of ultrasonography on these patients are shown in Table II. The common bile duct could be measured in 16 cases, in 12 it was dilated and, in four it was of normal diameter. Multiple dilated intrahepatic ducts were found in 16 cases and in four cases, dilated intrahepatic ducts were found in association with a normal common duct.

A dilated gallbladder was noted in 70% of the cases with dilated biliary ducts. Contrary to the clinical impression that a palpable gallbladder points strongly to a malignant process, in our series a dilated gallbladder, visible by ultrasound, was associated with a benign process in 30% of cases. Of the 20 cases with dilation of either the intrahepatic or extrahepatic ducts, the correct site of obstruction was identified in every instance but the exact nature of the obstruction was not determined. The single patient in whom ultrasonography failed to correctly predict that obstruction was present was an individual in whom jaundice was secondary to chronic pancreatitis. In this patient, the common bile duct measured 1 cm. in diameter and the intrahepatic ducts and gallbladder could not be visualized.

The results of ultrasonography in patients without biliary obstruction are shown in Table III. In three patients, both normal extrahepatic and intrahepatic ducts were seen. In three cases, visualization of only the intrahepatic ducts was successful, while in three other patients, only the common bile duct was seen.

Standard radiographic procedures were of limited diagnostic value in the group of patients treated. Plain abdominal roentgenography revealed right upper quadrant calcifications in three of 20 cases and in only one of these were gallstones the cause of obstruction. Barium upper gastrointestinal series revealed an abnormal duodenal C-loop in five of 20 cases. Three of these were associated with pancreatic carcinoma and one with pancreatic pseudocyst. The liver scan was useful in eight of 31 instances. In four cases, large filling defects representing primary or metastatic malignancy were found and in four cases a dilated *porta hepatis* was seen which correlated well with dilated bile ducts observed by ultrasound.

COMMENT

This study illustrates that ultrasonography has a definite place in the evaluation of patients with jaundice of uncertain etiology and in the decision-making process for patients with surgical jaundice. Ultrasonography has several distinctive advantages: it can be performed at any time and it can be applied equally well to the asymptomatic as to the severely ill patient. Ultrasonography is inexpensive and provides immediate information from which

TABLE III

RESULTS OF ULTRASONOGRAPHY IN PATIENTS WITHOUT EXTRAHEPATIC BILIARY OBSTRUCTION

Diagnosis	Ducts visualized (no.of patients)		
	Intrahepatic only	Common only	Both
Pancreatitis	2	0	0
Alcoholic hepatitis	1	2	1
Hepatoma	0	1	0
Toxic hepatitis	0	0	1
Sarcoid of liver	0	0	1

These observations were based on a total of 9 patients.

further diagnostic and therapeutic decisions can be made. The primary limitation of the usefulness of this procedure is the lack of a sufficient number of highly skilled ultrasonographers.

Gray Scale ultrasonography has greatly improved the ability of the ultrasonographer to identify the structures in the biliary tree.[10, 11] Without Gray Scale, the ultrasonographer had to rely primarily on the finding of an enlarged gallbladder as evidence of obstructive jaundice,[12] whereas now the intrahepatic ducts and the common bile duct can be scrutinized in most patients. Previous studies of the usefulness of ultrasound in the evaluation of the patient with obstructive jaundice did not report separate analysis of the three divisions of the biliary tree,[12, 13] the gallbladder, the common bile duct and the intrahepatic ducts. This study confirms the usefulness of ultrasound in correct identification of whether mechanical obstructive jaundice is present and agrees with Taylor, et al[13] that the correct differentiation can be made in more than 90% of patients. Taylor and Carpenter[11] emphasized that the presence of a dilated gallbladder alone is insufficient evidence for confirmation of diagnosis of obstructive jaundice and pointed out that dilated intrahepatic and extrahepatic ducts should also be explored.

We believe that the intrahepatic ducts should receive careful scrutiny since we found that a dilated common duct was not associated with normal intrahepatic ducts and a normal common bile duct was found in one-third of the cases of obstructive jaundice in which dilated intrahepatic ducts were identified. The diameter of ducts which successfully differentiate obstructive from non-obstructive jaundice (common bile duct $\geqq$ 1.4 mm., intrahepatic ducts $\geqq$ 4 mm. in diameter) were established by a retrospective analysis of our cases and, as such, must be verified by further experience.

The inability of ultrasonography to visualize areas of interest remains a problem. This nonvisualization can usually be attributed to excessive bowel gas, obesity, or barium within the gastrointestinal tract. In many cases, a follow-up examination will allow visualization of the biliary tree and pretreatment with oral simethicone may be of value in these patients. We believe that ultrasonography has a definite place in the evaluation of the icteric patient and should be considered as a useful adjunct to other studies. It is useful, not only in defining the site of obstruction in cases with obstructive jaundice but also in correctly categorizing patients with jaundice of uncertain etiology. Ultrasonography can also assist in the decision-making process required for planning the diagnostic and therapeutic approach toward patients with jaundice.

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Communication from Abroad

Endoscopic Papillotomy and Removal of Gallstones[*][†]

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Endoscopic papillotomy or EPT, has been used in Europe for over three years. It became a useful and successful procedure in high risk patients having gallstones in the common bile duct or papillary stenosis. In some meetings with experienced experts in surgery we have elaborated the following indications: 1. Retained calculi in the common bile duct after cholecystectomy. 2. Papillary stenosis or stenosis of the choledochus sphincter without narrowing of the pancreatic duct.

At our last meeting nine months ago high risk patients with concrements in the common bile duct, clinical symptoms and laboratory findings of bile duct obstruction, who have a gallbladder, were added to this list. Patients younger than 50 years of age and older patients in good condition may be sent to surgery. In some groups, the experienced endoscopist can perform EPT in small obstructing papillary tumors to restore the outflow of the bile prior to surgery because the risk of the operation can be reduced when the jaundice disappears.

MATERIAL AND METHOD

In selected patients as the first step, ERCP is performed to confirm the diagnosis and to clarify exactly the technical details of the management. After verification of the pathological findings a special high-frequency knife, developed in Germany and commonly used in our country, is inserted via a duodenoscope into the distal common bile duct and the roof of the papilla is incised. After cutting the papilla in most of the cases the concrements are collected in the distal part of the common bile duct. When the stones are located

TABLE I

ENDOSCOPIC PAPILLOTOMY (EPT) IN WEST GERMANY

Endoscopy unit	Tried	Succeeded
Classen, Wurbs (Hamburg)	146	137 (93.8%)
Demling, Koch-Rösch (Erlangen)	159	151 (99.0%)
Manegold (Mannheim)	62	55 (88.7%)
Ottenjann (Munich)	104	94 (90.4%)
Paul (Giessen)	20	18 (90.0%)
Safrany (Münster)	338	312 (92.3%)
Seifert (Wilhelmshaven)	61	56 (91.8%)
Soehendra (Hamburg)	47	43 (91.5%)
Stadelmann (Fürth)	18	14 (77.8%)
Totals	955	880 (92.1%)

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[*] Read before the 41st Annual Convention of the American College of Gastroenterology, Montreal, Canada, 25, 26, 27 October 1976.

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TABLE II

ENDOSCOPIC PAPILLOTOMY (EPT) IN WEST GERMANY

Endoscopic unit	No.	Indications: Choledocholithiasis: Cholecystectomized	Gallbladder *in situ*	Tot.	Stenosis	Tumor	Others
Classen, Wurbs (Hamburg)	137	74	46	120	13	4	—
Demling, Koch-Rösch (Erlangen)	159	97	46	143	16	—	—
Manegold (Mannheim)	62	43	15	58	3	—	1
Ottenjann (Munich)	94	85	2	87	—	—	7
Paul (Giessen)	18	15	3	18	—	—	—
Safrany (Münster)	312	181	44	225	81	6	—
Seifert (Wilhelmshaven)	61	36	11	47	10	—	4
Soehendra (Hamburg)	43	35	1	36	5	2	—
Stadelmann (Fürth)	14	6	3	9	4	—	1
Totals	900	572 (77%)	171 (23%)	743 (82.6%)	132 (14.7%)	12 (1.3%)	13 (1.4%)

TABLE III

RESULTS OF ENDOSCOPIC PAPILLOTOMY (EPT) IN CASES WITH CHOLEDOCHOLITHIASIS IN WEST GERMANY

Endoscopic unit	No.	Spontaneous delivery	Extraction	Negative or incomplete	No control
Classen, Wurbs (Hamburg)	120	80	14	17	9
Demling, Koch-Rösch (Erlangen)	143	69	56	8	10
Manegold (Mannheim)	55	37	11	7	–
Ottenjann (Munich)	78	55	5 (lavage 3)	12	3
Paul (Giessen)	18	7	2	2	7
Safrany (Münster)	225	126	84	13	2
Seifert (Wilhelmshaven)	47	27	11 (+ spont. 3)	4	2
Soehendra (Hamburg)	36	11	11 (+ spont. 7)	6	1
Stadelmann (Fürth)	9	9	–	–	–
Totals	731	421 (57.6%) (85.9%)	207 (28.3%)	69 (9.4%)	34 (4.7%)

close to the cut papilla a specially designed Dormia basket may be used for the immediate stone extraction. When the stone is located in the upper common bile duct the group of Ottenjann in Munich and our group like to insert an indwelling tube into the duct trying to lavage the stones using sodium cholate or lidocaine. This procedure for dissolving retained stones after surgery via a T-tube, was described by Britton, Lansford and Toouli in 1974 and 1975. But now the usual mèthod in Germany is to wait for a spontaneous delivery. When this is not observed within one week we re-examine the patient by ERCP and try to extract the stones via a Dormia basket. Another procedure of gallstone removal consists of inserting the cannulation tube into the stoma and performing EPT. If after papillotomy the stoma is opened wide a long cannulating tube is re-inserted. The tube remains in the common bile duct and the duodenofiberscope is removed pushing the tube step by step through the instrumentation channel of the fiberscope. If after one week no spontaneous delivery

TABLE IV

COMPLICATIONS, DETECTION OF SYMPTOMS AFTER EPT IN 880 CASES

Kind of complication	0 hr.	24 hr.	36 hr.	48 hr.	?	Total
Hemorrhage	11	3	—	—	2	16 (25%)
Perforation	12	—	—	—	1	13 (20%)
Cholangitis	—	8	1	2	2	13 (20%)
Pancreatitis	—	4	2	1	8	15 (24%)
Stone impaction	3	—	1	1	1	6 (9%)
Impaction of Dormia basket	1	—	—	—	—	1 (2%)
Totals	27 (42%)	15 (24%)	4 (6%)	4 (6%)	14 (22%)	64 (7.3%)
	42 = 66%		8 = 12%			

TABLE V

TREATMENT OF COMPLICATIONS AFTER EPT

Kind of complication	Conservative	Endoscopically	Operative	Total
Hemorrhage	12	—	4	16
Perforation	9	—	4	13
Cholangitis	6	1	6	13
Pancreatitis	14	—	1	15
Stone impaction	1	2	3	6
Impaction of Dormia basket	—	—	1	1
Totals	42 (65%)	3 (5%)	19 (30%)	64

of the stone is observed, the fiberscope is inserted once more. The Dormia basket is inserted alongside the tube and the stone is removed from the papilla.

RESULTS

It is necessary to control the success of EPT three to six months following EPT to confirm that the stoma is open. The results of EPT in West Germany from nine centers in the past until the end of August, 1976 are shown in Table I. EPT was tried in 955 cases and succeeded in 880 cases (92.1%). The success rate was not significantly different in the nine centers. Choledocholithiasis was the most frequent indication in 82.6% (Table II). Out of 743 cases 77% of the patients chole-

TABLE VI

ENDOSCOPIC PAPILLOTOMY (EPT No. = 880) MORTALITY No. = 15 = 1.7% (1.25%)

Endoscopy unit	Complication	Treatment	Cause of death
Classen, Wurbs (Hamburg)	Hemorrhage Pancreatitis	Operative Conservative	Hemorrhage Lung infarct
Demling, Koch-Rösch (Erlangen)	Stone impaction	Operative	Septicemia Liver abscesses
Manegold (Mannheim)	– – –	– – –	Toxic cardiac failure Toxic cardiac failure Toxic cardiac failure
Ottenjann (Munich)	Cholangitis –	Conservative –	Toxic cardiac failure Cardiac failure
Paul (Giessen)	–	–	–
Safrany (Münster)	Pancreatitis Cholangitis Cholangitis	Conservative Conservative Operative	Pancreatitis Septicemia Septicemia
Seifert (Wilhelmshaven)	Perforation (S) Perforation (S) Stone impaction (?)	Operative Operative Conservative	Peritonitis Pancreatitis Cholangitis
Soehendra (Hamburg)	–	–	–
Stadelmann (Fürth)	Pancreatitis	Conservative	Pancreatitis

cystectomized and in 23% the gallbladder was present. In 14.7% a papillary stenosis was the indication for EPT. In 12 cases of a papillary tumor, EPT was performed in 1.3%. Out of 731 cases with choledocholithiasis a spontaneous delivery of the stones was observed in 57.6% and an extraction was performed in 28.3% (Table III). Therefore the success rate was 85.9%. In 9.4%, the results were negative or incomplete. Incomplete means that in high-risk-patients a delivery of stones out of the common bile duct was impossible but jaundice disappeared and the papillotomystoma was proved to be open endoscopically. In 4.7% of the patients no control was done. In 64 out of 880 cases (7.3%) we had complications (Table IV). We had hemorrhage in 16, perforation with the diathermy knife or the Dormia basket in 13 cases. In 13 patients a cholangitis and in 15 patients a pancreatitis followed EPT. A special complication of EPT is the stone impaction following the procedure which was observed in six cases. In one case the Dormia basket became impacted into the common bile duct and had to be removed surgically. Most of the complications developed within 24 hours after the procedure. Only

12% were seen on the second day. In 22% of the complications an exact determination of the time between the procedure and the development of the symptoms was not clarified. Sixty-five per cent of the complications were treated conservatively, 5% endoscopically and 30% by surgery (Table V). Therefore, it may be supposed that EPT should only be done in patients who are also operable. Most of the hemorrhages could be stopped conservatively. We have treated nine out of our 13 perforations conservatively. But in most of these cases only a small amount of contrast material was found after EPT, outside of the duct system and in many cases only slight clinical symptoms developed. Therefore, our proceeding after visible perforation by EPT depends on the clinical course. Cholangitis was seen only in cases when larger stones remained after EPT. This complication may be reduced by introduction of an indwelling tube in the common bile duct immediately after EPT. All cases of pancreatitis, except one, were treated conservatively. Stone impaction is one of the special complications of EPT. After a few hours a severe cholangitis may develop. This dangerous complication should be kept in mind and all patients in whom the concrements are not removed immediately after EPT have to be observed carefully within the next days. When clinical symptoms of a cholangitis occur the patient must be operated upon or the stone should be removed endoscopically within the next few hours. The impaction of a Dormia basket is a rare complication and was observed in only one case. The mortality rate was 1.7% in our series (Table VI). When you exclude those cases who died of cardiac failure which was independent from the EPT, this rate is reduced to 1.25%. All the complications mentioned above may have a fatal outcome. Five out of 11 lethal complications were treated surgically, six conservatively.

SUMMARY

Summarizing our results we come the following conclusions:

1. In high risk but operable patients, EPT is a useful treatment in cases with choledocholithiasis and with papillary stenosis.

2. The risk of the procedure is lower than by surgical intervention.

3. Complications can occur in 7.3%, most of them within 24 hours.

4. The mortality rate was 1.7% and depends on the precise selection of the patients; on the knowledge of the post-papillotomy treatment and on the experience of the examiner.

5. This procedure, at the present time, should be limited to centers with well trained and experienced endoscopists.

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Gallstone Dissolution by Chenodeoxycholic Acid and Phenobarbital*

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Gallstone dissolution and biliary lipids were determined and compared in patients receiving either chenodeoxycholic acid (CDC), or CDC and phenobarbital (PB) for 1½ to 2 years. Among patients with radiolucent gallstones, dissolution occurred in 53% of those receiving CDC alone and in only 25% of those receiving both CDC and PB. No dissolution occurred in 13 other patients with calcified gallstones. Patients with dissolution had a significantly greater molar percentage of CDC and a significantly lower saturation index in bile than those without dissolution. Diarrhea and transiently abnormal liver function tests were the most frequently observed side-effects but only diarrhea necessitated a reduction of the CDC dose. Gallstones recurred following dissolution in one of six patients followed for six months after discontinuation of CDC. In conclusion, PB did not enhance CDC-induced desaturation of bile or gallstone dissolution.

INTRODUCTION

Oral administration of chenodeoxycholic acid (CDC) decreases biliary cholesterol saturation and dissolves cholesterol gallstones.[1-3] Phenobarbital (PB) also decreases biliary cholesterol saturation, although to a lesser degree than CDC[4] and alone does not dissolve gallstones.[4, 5] The aim of the present study was to determine whether PB enhances CDC-induced gallstone dissolution.

METHODS

Experimental design:—Sixty-seven patients with radiolucent or calcified gallstones visualized on oral cholecystography entered the study after giving informed consent. The women were either postmenopausal or posthysterectomy. Each patient was randomly allocated to receive in double-blind fashion either CDC, 750 mg./d. and PB, 200 mg./d. or CDC and PB placebo for 1½-2 years or until gallstone dissolution was complete. PB was given as a single daily dose at bedtime while CDC was given as a divided dose following breakfast, lunch and dinner. CDC obtained from Weddel Pharmaceuticals, London, England, via Rowell Laboratories, Inc., Baudette, MN, contained 96.7% CDC and less

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TABLE I

GALLSTONE DISSOLUTION WITH CALCIFIED (CA^{++}) AND RADIOLUCENT GALLSTONES DURING TREATMENT WITH EITHER CDC OR CDC AND PB.

	CDC	CDC + PB
Ca^{++}	0/9	0/4
Lucent	10/19	4/16

than 0.1% lithocholic acid as determined by gas liquid chromatography. PB was obtained from Eli Lilly and Company. Lactose was used as the placebo.

Serum glutamic oxalacetic transaminase (SGOT), alkaline phosphatase and bilirubin were determined initially and every three months while urinalysis, hematocrit, white blood cell count and serum levels of triglyceride, cholesterol and creatinine were obtained every six months. Oral cholecystograms were done and fasting gallbladder bile was obtained (via cholecystokinin stimulated, duodenal, biliary drainage) initially and after six months, one year, and 1½-2 years of treatment. At 1½-2 years the cholecystograms were read and compared without knowledge of the patient's name or treatment group. If by this time partial dissolution (50%) had occurred, treatment was continued. When dissolution was complete, treatment was continued for three months and a follow-up cholecystogram was obtained six months after discontinuing treatment.

Biliary lipid analyses:—Immediately following biliary drainage, aliquots of each bile sample were apportioned to the appropriate solvents for lipid analyses. The biliary composition of each sample was determined. Total bile acids were measured by the steroid dehydrogenase method of Talalay.[6] Phospholipids were measured by the colorimetric method of Fiske and Subbarow.[7] Cholesterol and individual bile acids were measured by gas-liquid chromatography as previously described.[8] Sulfated bile acids were not determined.

The molar percentage of cholesterol was calculated as follows: moles of cholesterol/(moles of cholesterol + moles of total bile acids + moles of phospholipid) × 100. The molar percentages of phospholipid and total bile acids were calculated in a similar manner. The molar percentages of individual bile acids were expressed as percent of total bile acids. The degree of cholesterol saturation of bile was expressed as the saturation index as used by Thomas and Hofmann[9] and was calculated using the limit of biliary cholesterol saturation as defined by Holzbach and colleagues.[10]

For comparing biliary lipids between groups during treatment the values from each patient's last biliary drainage were used. Statistical significance was determined with the Student's "t" test.

RESULTS

Age, sex ratio, body weight and mean saturation index were similar in the two treatment groups at randomization.

Compliance:—Forty-eight (72%) of the 67 patients completed the study, 28 in the CDC group and 20 in the CDC and PB group. The difference in patient numbers is explained by the misrandomization of two patients and the dropping out of three more patients from the CDC and PB groups. The reasons for dropping out of the study were similar in each of the two treatment groups. Twelve patients dropped out of the study because of inability or unwillingness to continue in the program while six underwent cholecystectomy (two for biliary colic, two for cholecystitis and two incidental to other operations). One patient was dropped from the study when cirrhosis was found on liver biopsy. Only

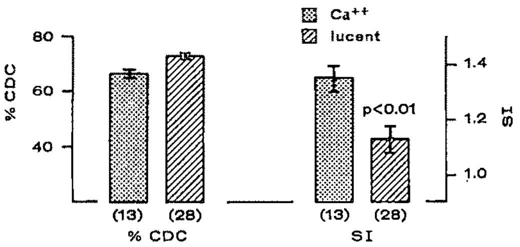

Fig. 1—Molar percentage of biliary CDC and saturation index (SI) in patients with calcified (Ca^{++}) and radiolucent gallstones during CDC treatment. The number of bile samples analyzed is shown in parentheses.

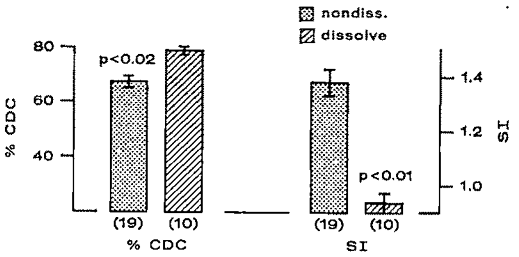

Fig. 2—Molar percentage of biliary CDC and saturation index (SI) in radiolucent gallstone patients with and without dissolution during CDC treatment. The number of bile samples analyzed is shown in parentheses.

data from patients who completed the study were evaluated.

Of the patients who completed the study, four in the CDC group and two in the CDC and PB group took only 500 mg. of CDC. Seven patients in the CDC and PB group and 10 patients in the CDC group discontinued PB or the PB placebo respectively. Five patients in the CDC and PB group reduced the dose of PB to 100 mg./d. while only one patient in the CDC group reduced the dose of PB placebo.

Dissolution:—None of the 13 patients with calcified gallstones had dissolution (Table I). In the patients with radiolucent gallstones, 10 of 19 randomized to the CDC group had dissolution (nine complete, one partial) while only four of 16 randomized to the CDC and PB group had dissolution (three complete, one partial) but the difference was not statistically significant. Furthermore, in two of the four with dissolution receiving CDC and PB, dissolution did not begin until six months and one year after PB was discontinued. Clearly, phenobarbital did not enhance CDC-induced dissolution. There was no difference between the two treatment groups with regard to gallstone size or presence of multiple gallstones. Although dissolvers and nondissolvers received comparable milligram doses of CDC, the mean weight of the dissolvers was less than that of the nondissolvers and they therefore received a significantly larger mg./kg. dose (12.9 ± 0.5 vs. 9.8 ± 1.1, p 0.02).

Biliary lipids:—Prior to treatment the saturation indices were similar in the calcified and noncalcified gallstone patients, although the molar percentage of CDC was significantly greater ($P < 0.01$) in the calcified (38.1 ± 0.2) than in the noncalcified (31.1 ± 1.4) gallstone patients. After treatment (Fig. 1) the molar percentages of CDC were similar in the calcified and noncalcified gallstone patients but the saturation index was significantly greater in the calcified gallstone patients.

Prior to treatment, the molar percentages of CDC and the saturation indices were similar when radiolucent gallstone patients with and without dissolution were compared. After treatment (Fig. 2), radiolucent gallstone patients with dissolution had a significantly greater molar percentages of CDC and a significantly lower saturation index than radiolucent gallstone patients without dissolution.

Prior to treatment, the saturation indices and the molar percentages of CDC, lithocholic acid, total bile acids, cholesterol and phospholipid were similar when radiolucent gallstone patients receiving

TABLE II

Biliary Lipids in Radiolucent Gallstone Patients Receiving Either CDC or CDC and PB

	BA	C	PL	CDC	L	SI
CDC n = 19	70.6 ± 3.3	7.2 ± 0.3	21.0 ± 3.5	74.8 ± 6.0	3.7 ± 0.4	1.10 ± 0.07
CDC + PB n = 11	72.1 ± 3.5	6.9 ± 0.6	21.0 ± 1.0	72.1 ± 4.8	4.3 ± 0.6	1.04 ± 0.11

All values are expressed as mol. % ± SEM. BA = total bile acids; C = cholesterol; PL = phospholipid; L = lithocholic acid; SI = saturation index.

CDC alone were compared with patients receiving CDC and PB (Table II). For this and all subsequent comparisons, patients who discontinued PB were included with the CDC alone group. After treatment, biliary lipid composition and saturation indices in the two groups remained similar.

Side-effects and toxicity:—CDC:—During treatment, diarrhea and/or abdominal cramps necessitated a reduced dose of CDC (500 mg./d.) in four patients from the CDC group and two from the CDC and PB group. Biliary colic occurred in 20-30% of patients and was not more frequent in patients with or without dissolution. Eight patients from the CDC group and six from the CDC and PB group developed transiently elevated (less than twice normal) SGOT, alkaline phosphatase, or both. The molar percentage of lithocholic acid was similar in patients with and without abnormal tests. Serum cholesterol and triglycerides did not change in either treatment group.

Phenobarbital:—The reason for discontinuing or reducing the dose of phenobarbital was morning drowsiness in all but one patient who developed a skin rash that cleared following discontinuation of phenobarbital.

Recurrence:—Six of the 12 patients with complete dissolution have had cholecystograms six months after discontinuation of treatment, and in one of these patients gallstones were again seen.

Comment

Our experience with patients treated with CDC alone is in agreement with that of other workers.[11, 12] Thistle, et al[11] found a dissolution rate of 48% in radiolucent gallstone patients treated with 15 mg./kg. of CDC, a value similar to our 53%. CDC treated patients with dissolution had bile that was cholesterol unsaturated or very nearly so (saturation index range of 0.59 to 1.16) while only one patient with unsaturated bile (saturation index of 0.90) did not have dissolution. The poor results in calcified gallstone patients as also found by Thistle and Hofmann[13] might have been due in our study to resistance to the cholesterol-desaturating effects of CDC. Iser, et al,[12] however, have had similarly poor results in radiopaque gallstone patients who develop cholesterol unsaturated bile.

Diarrhea and transiently abnormal liver function tests were the most frequently observed side-effects but only diarrhea necessitated a reduction of the CDC dose. CDC treatment had no effect on serum cholesterol or triglyceride levels. In addition we found no evidence that dissolution is associated with the development of gallstone complications since abnormal liver function tests, biliary colic and cholecystitis occurred with equal frequency in patients with and without dissolution. Gallstones recurred following dissolution in one of six patients followed for six months after discontinuation of CDC.

Phenobarbital decreases biliary cholesterol saturation and the prevalence of biliary cholesterol crystals in patients with cholesterol gallstones,[4, 5] presumably by increasing bile pool size and bile flow.[5, 14, 15] Bile, however, does not become cholesterol unsaturated and gallstone dissolution does not occur.[4, 5] Although the combination of PB and CDC does not cause increased lowering of biliary cholesterol saturation than CDS alone, a prior study from our laboratory did not exclude the possibility that PB might enhance CDC-induced gallstone dissolution.[4] Accordingly, that study was expanded to further explore this interaction. In this study we have found that PB does not enhance CDC-induced biliary cholesterol desaturation or gallstone dissolution. The apparent inhibition of CDC-dissolution by PB was not statistically significant. The power, however, to detect a difference at the 0.05 level between 25% dissolution in 16 patients receiving CDC and PB and 53% dissolution in 19 patients receiving CDC alone is less than 45%.[16] Although PB does not enhance CDC-induced dissolution, it should be evaluated in cholesterol gallstone prophylaxis.

Lithocholic acid, formed solely in the distal intestine by the bacterial 7 alpha dehydroxylation of CDC, is found in increased proportions in patients receiving CDC and has been suggested as the cause of CDC-associated animal hepatotoxicity and human liver function test abnormalities. In our previous study[4] we found that PB prevented the increase in the proportion of biliary lithocholic acid during CDC treatment and speculated that PB might thus protect against potential CDC hepatotoxicity. In the present study we found no prevention of the rise in lithocholic acid by PB and no association of abnormal SGOT or alkaline phosphatase with high biliary lithocholic acid levels. It has recently been determined, however, that sulfated lithocholic acid is a major metabolite of lithocholic acid and therefore the measurement of the nonsulfated compound alone would incompletely reflect the formation, absorption and re-excretion of lithocholic acid.

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Communication from Abroad

Human Exocrine Pancreatic Response with Different Types of Secretin

INFLUENCE OF SEX, AGE, AND PREVIOUS INTRADUODENAL SORBITOL INFUSION

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A comparative analysis of the exocrine pancreatic secretion response with three different kinds of impure secretin was performed. Two series, carried out in Buenos Aires (Vitrum and Boots secretin), were compared with the Dreiling series (Lilly secretin) done in New York. All tests were performed with a single I.V. submaximal (1 U./kg.) dose of the hormone and with the same Dreiling technic. The evaluation showed: 1. The absence of significant differences in men among the three series. 2. Contrary to the results with the Lilly product, with both the Boots and Vitrum secretin the hydrelatic but not the ecbolic values are significantly greater in men than in women. This seems to reflect a sex-linked different sensitivity to secretin of the "pancreon" units. 3. Either in men or women the pancreatic secretion is not influenced by the age of the individual. 4. The Boots secretin results are not modified by the previous sorbitol intraduodenal infusion.

The aim of this study was to disclose whether or not the exocrine pancreatic response evoked by single submaximal intravenous (I.V.) injections of secretin was influenced by the source of the hormone, the sex and age of the patients. Another purpose of this analysis was to elucidate whether or not the secretin-induced response is influenced by the previous intraduodenal infusion of sorbitol, a monosaccharide widely used by us as an endogenous CCK-PZ releaser from the "trigger zone" of the "pancreon" units.[1, 2] The brands of secretin that were analyzed are impure and were those that were available in Buenos Aires at the time of this study. Three series were scrutinized. All tests were carried out with the same Dreiling technic.[3] Two were performed in the Clinicas Hospital, (Vitrum and Boots secretin). These results were compared with those obtained by Dreiling at the Mount Sinai Hospital. (Lilly secretin).[4]

MATERIAL AND METHODS

The secretin tests analyzed were those performed in subjects who had no known history of pancreatic disease, on physical examination or by laboratory criteria. The Dreiling technic[3] was followed in all cases. After duodenal intubation with a double lumen tube (Dreiling), gastric and duodenal juices were collected separately. After a 20-minute control collection period, secretin was injected as a single bolus injection at the standard dose of 1 U./kg. Total duodenal collection was made over a period 80 minutes. The four initial samples were of 10 minutes each, followed by two of 20 minutes each. The hydrelatic response was measured by the following parameters: 1. total volume in 80 minutes (ml.); 2. total volume in 80 min./kg. body

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TABLE I

COMPARATIVE ANALYSIS OF THE HYDRELATIC PANCREATIC SECRETION RESPONSE USING THREE DIFFERENT SOURCES OF SECRETIN: LILLY, VITRUM AND BOOTS (1 U./KG.), MEN, ALL AGES

	Lilly secretin (41 subjects) Dreiling's series mean age: 56.4			Vitrum secretin (11 subjects) our series mean age: 48.1			Boots secretin (25 subjects) our series mean age: 48.3		
	Mean	S.D.	Coeff. var. (%)	Mean	S.D.	Coef. var. (%)	Mean	S.D.	Coef. var. (%)
Total vol. 80 min. (ml.)	230	80	35.0	232	78.2	33.0	222	79	36
Total vol. 80 min./kg. (ml./kg.)	3.56	1.22	35.0	3.6	1.07	29.0	3.02	1.33	44.0
Peak 10 min. vol. (ml.)	52.4	16.6	32.0	66.5	29.7	45.0	50.0	14.1	28.1
Peak HCO_3 conc. (mEq./l.)	109.6	11.75	10.7	119	17.70	14.0	117*	9.3	7.9
Total 80 min. HCO_3 output (mEq.)	20.6	8.25	54.0	22.5	7.8	34.60	21.04	9.5	45.0
Peak 10 min. HCO_3 output (mEq.)	5.05	1.73	40.0	6.52	1.94	30.0	5.07	1.55	30.0

* $P < 0.05$ Significant difference compared with the New York series (Dreiling)

TABLE II

COMPARATIVE ANALYSIS OF THE HYDRELATIC PANCREATIC SECRETION RESPONSE USING THREE DIFFERENT SOURCES OF SECRETIN: LILLY, VITRUM AND BOOTS (1 U./KG.) WOMEN, ALL AGES

	Lilly secretin (62 subjects) Dreiling's series mean age: 48.5			Vitrum secretin (14 subjects) our series mean age: 36.5			Boots secretin (25 subjects) our series mean age: 49.2		
	Mean	S.D.	Coef. var. (%)	Mean	S.D.	Coef. var. (%)	Mean	S.D.	Coef. var. (%)
Total vol. 80 min. (ml.)	212	55.7	26.0	183	65.4	36.0	185	62	33.5
Total vol. 80 min./kg. (ml./kg.)	3.8	1.1	29.0	2.78	0.92	33.0***	3.0	0.95	31.6***
Peak 10 min. vol. (ml.)	51.4	16.2	31.5	43.9	12.9	29.0	39.7	10.7	26.0***
Peak HCO_3 conc. (mEq./l.)	107.4	10.0	9.3	114	13.9	12.0**	110	9.5	8.6
Total 80 min. HCO_3 output (mEq.)	18.2	11.2	61.5	15.9	6.6	41.0	16.4	5.8	35.0
Peak 10 min. HCO_3 output (mEq.)	4.67	1.58	33.8	4.31	1.14	26.0	3.87	1.2	31.0**

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Significant differences compared with the New York series (Dreiling).

weight (ml./kg.); 3. peak 10-minute volume (ml.); 4. peak bicarbonate concentration (mEq./l.); 5. total bicarbonate output in 80 minutes (mEq./80 min.); 6. peak 10-minute bicarbonate output (mEq./10 min.). The pancreatic ecbolic response was determined by: 1. amylase, total units in 80 minutes (Somogyi U./80 min.); 2. amylase, total units per kilogram body weight; 3. peak lipase concentration (Bang).[5]

Lipase[5] was measured in three samples. The first two were of 20 minutes each and the last one was of 40 minutes.

In both series with Vitrum and Boots secretin, a group of patients was subjected before the I.V. injection of the hormone to an intraduodenal infusion of sorbitol (20 gm.) dissolved in 70 ml. of water. The solution was brought to body temperature and was infused in a 5-minute period, keeping the syringe at bed level. Gastric suction was pursued but the duodenal collection was arrested for 10 minutes. When the latter was restarted a pure bile-tainted duodenal juice was obtained. At this moment the gallbladder contraction may be evident or not. Bromsulfthalein (BSP), either the full dose (5 mg./kg.) or just 1 or 2 ml. was injected I.V. in order to determine the bile excretion time of the dye in the duodenum (combined BSP-secretin test).[6] When the full BSP dose is administered, a simultaneous liver clearance of the dye may be performed. In a long and large experience with sorbitol we have shown that this monosaccharide does not modify the bicarbonate concentration and raises the amylase and lipase concentration and output in the duodenal juice. The postsorbitol response was divided into three samples of 10 minutes each. At this moment the secretin test was performed as usual. In order to determine whether or not sorbitol influences the secretin-induced response, a comparative

TABLE III

COMPARATIVE ANALYSIS OF WEIGHT DISTRIBUTION IN THREE SECRETIN SERIES

	a. Lilly secretin (Dreiling's series)			b. Boots secretin (our series)				Statistical differences	c. Vitrum secretin (our series)				Statistical differences	
No. subj.	Range	Mean	S.D.	No. subj.	Range	Mean	S.D.	b.v.a. (P)	No. subj.	Range	Mean	S.D.	c.v.a (P)	c.v.b (P)
In females (all ages)														
62	35-100	56.3	10.2	25	47-88	62.7	10.6	< 0.01*	14	52-84	60.7	9.6	> 0.1	> 0.3
In males (all ages)														
41	42-87	63.9	13.8	25	57-106	73.04	10.2	< 0.002*	11	55-87	64.2	11.8	> 0.8	< 0.05*

* Statistically significant difference ($P < 0.05$).

TABLE IV

Comparative Analysis, Men Versus Women, of the Hydrelatic Pancreatic Secretion Response Obtained with Vitrum Secretin

	Men (all ages) Mean age: 48.1 Range: 30-75 S.D.: 15.29 (11 subjects)	Women (all ages) Mean age: 36.9 Range: 25-62 S.D.: 20.5 (14 subjects)	"t"	P
			3.6	< 0.001*
Total vol. 80 min. (ml.)	232	183	1.71	> 0.1
Total vol. 80 min./kg. (ml./kg.)	3.6	2.78	2.65	< 0.02*
Peak 10 min. vol. (ml.)	66.5	43.9	2.53	< 0.02*
Peak HCO_3 conc. (mEq./l.)	119	114	0.77	> 0.4
Total 80 min. HCO_3 output (mEq.)	22.5	15.9	2.23	< 0.05*
Peak 10 min. HCO_3 output (mEq.)	6.5	4.31	3.47	< 0.01*

* Significant difference ($P < 0.05$)

TABLE V

Comparative Analysis, Men Versus Women, of the Hydrelatic Pancreatic Secretion Response Obtained with Boots Secretin

	Men (all ages) Mean age: 48.3 Range: 21-81 S.D.: 14.31 (25 subjects)	Women (all ages) Mean age: 49.2 Range: 23-66 S.D.: 11.87 (25 subjects)	"t"	P
			0.24	> 0.8
Total vol. 80 min. (ml.)	222	185	1.85	> 0.05
Total vol. 80 min./kg. (ml./kg.)	3.02	3.0	0.06	> 0.9
Peak 10 min. vol. (ml.)	50	39.7	2.87	< 0.01*
Peak HCO_3 conc. (mEq./l.)	117	110	2.64	< 0.01*
Total 80 min. HCO_3 output (mEq.)	21.04	16.40	2.08	< 0.05*
Peak 10 min. HCO_3 output (mEq.)	5.07	3.87	3.04	< 0.01*

* Significant difference ($P < 0.05$)

TABLE VI

Comparative Analysis of the Hydrelatic and Ecbolic Secretion Response with Boots Secretin in Men Above and Below the Age of 50

	< 50 years (25 subjects)			> 50 years (25 subjects)			"t"	P
	Mean	S.D.	Mean ± 2 S.D.	Mean	S.D.	Mean ± 2 S.D.		
Total vol. 80 min. (ml.)	200	53.6	308 93	249	108	465 33	1.47	NS
Total vol. 80 min./kg. (ml./kg.)	2.65	0.91	4.47 0.83	3.48	1.65	6.78 0.18	1.59	NS
Peak 10 min. vol. (ml.)	48.2	12.56	73.22 23.08	52.40	16.27	84.94 19.86	0.72	NS
Peak HCO_3 conc. (mEq./l.)	117	11.09	139 94.8	117	6.7	130 103.6	0.0	NS
Total 80 min. HCO_3 output (mEq.)	18.2	5.83	29.86 6.56	24.4	12.24	48.9 0.0	1.67	NS
Peak 10 min. HCO_3 output (mEq.)	4.7	1.19	7.08 2.32	5.5	1.87	9.24 1.70	1.29	NS
Total 80 min. amylase output (Somogyi U./80 min.)	1735	224.5	2184 1286	2308	894	4096 520	1.69	NS
Total 80 min. amylase output/kg. (U./kg.)	22.6	9.79	42.18 3.02	32.2	13.78	59.76 4.64	1.94	NS
Peak lipase concentration (Bang U./ml.)	1167	151	1469 865	1240	251	1978 738	0.12	NS

analysis was done of the secretin results obtained with and without a previous sorbitol infusion.

The statistical analysis was carried out with the "t" test[7] for nonpaired values; $P < 0.05$ was accepted as the level of significance.

RESULTS

The comparative analysis showed that in males the hydrelatic parameters values, with the only exception of peak bicarbonate concentration, were practically identical in the three secretin series (Table I). In women, on the other hand, the series performed in Buenos Aires, either with Vitrum or Boots secretin showed, in general, lower hydrelatic values than those obtained with Lilly secretin in New York (Table II).

Both in males and females, the average weight of subjects in the Boots series was higher than of those in the Lilly series. On the other hand, there were no differences in weight, both in males and females, between subjects of the Vitrum and the Lilly secretin series (Table III).

Contrary to the results observed with Lilly secretin,[4] with both Boots and Vitrum secretin the hydrelatic but not the ecbolic exocrine pancreatic secretion values were significantly higher in men than in women (Tables IV and V).

In agreement with the Dreiling findings,[4] the analysis made, both in males and females, with Boots secretin, between the results obtained above and below the arbitrary line drawn at the age of 50, showed that neither the hydrelatic nor the ecbolic pancreatic secretory responses were significantly different (Tables VI and VII).

A comparative analysis done in the Boots secretin series revealed that neither the hydrelatic nor the ecbolic pancreatic secretion responses were significantly influenced by a previous intraduodenal sorbitol infusion (Table VIII).

COMMENT

The present results show that in men, when applying the same Dreiling technic,[3] one can obtain very close exocrine pancreatic secretion values in two different countries using three different sources of impure secretin (Tables I and II).

Accepting Dreiling's dictum that the best diagnostic discriminative parameter is the one that gives the lowest coefficient of variation,[3] our findings have confirmed his contention that peak bicarbonate concentration is the parameter of choice (Tables I and II).

Contrary to the results of Rosenberg, et al,[4] our series showed that the hydrelatic but not the ecbolic values were significantly higher in men than in women. Christensen,[8] in 1963 and Perrier,[9] in 1966, both working with Vitrum secretin at the submaximal dose of 1 U./kg., found significantly higher hydrelatic values in men than in women. Hansky, et al,[10] in Dreiling's laboratory, attempted to compare their results in the dog with some in humans. To this end they analyzed 12 randomly selected normal subjects, six males and six females, as to their response to a standard secretin test (1 U./kg.). The mean peak 15-minute bicarbonate output was 6.9 (5.5-8.1) mEq. in the females and 8.2 (6.1-12.9) mEq. in the males. Mean body weight was the same for both groups, 61 (46-100) kg. in the females and 61 (50-75) kg. in the males. An interesting observation of this analysis was that the calculated bicarbonate output per gram of human pancreas was 0.08 mEq./gm. in the females and 0.09 mEq./gm. in the males and that the female dog excreted exactly the same amount of bicarbonate (0.08 mEq./gm.) as the female human.

TABLE VII

Comparative Analysis of the Hydrelatic and Ecbolic Pancreatic Secretion Responses with Boots Secretin in Women Above and Below the Age of 50

	< 50 years (25 subjects)			> 50 years (23 subjects)			"t"	P
	Mean	S.D.	Mean ± 2 S.D.	Mean	S.D.	Mean ± 2 S.D.		
Total vol. 80 min. (ml.)	177	54.7	286.4 67.6	193	68.5	330 56	0.65	NS
Total vol. 80 min./kg. (ml./kg.)	2.78	0.78	4.34 1.22	3.26	1.07	5.40 1.12	1.23	NS
Peak HCO_3 conc. (mEq./l.)	111.3	9.2	129.7 92.9	108.8	10.1	129 88.6	0.63	NS
Total 80 min. HCO_3 output (mEq.)	15.8	5.6	27.0 4.6	16.9	6.1	29.1 4.7	0.47	NS
Peak 10 min. HCO_3 output (mEq.)	3.76	1.0	5.76 1.76	3.99	1.4	6.79 1.19	0.45	NS
Total 80 min. amylase output (Somogyi U./80 min.)	1581	705	2993 171	1544	731	3006 82	0.12	NS
Total 80 min. amylase output/kg. (U./kg.)	24.6	10.57	45.74 3.46	25.70	11.0	47.70 3.70	0.24	NS
Peak lipase concentration (Bang U./ml.)	1389	503	2394 384	1275	406	2087 467	0.46	NS

TABLE VIII

COMPARATIVE ANALYSIS IN MEN AND WOMEN OF THE SECRETIN-INDUCED (BOOTS) ECBOLIC PANCREATIC SECRETORY RESPONSE OBSERVED WITH AND WITHOUT A PREVIOUS INTRADUODENAL SORBITOL INFUSION

	Men				Women			
	Sorbitol followed by secretin (15 subjects)	Secretin alone (8 subjects)	"t"	P	Sorbitol followed by secretin (7 subjects)	Secretin alone (17 subjects)	"t"	P
Total 80 min. amylase output (Somogyi)	2056 (856)	1850 (806)	1.76	NS	1545 (712)	1572 (719)	0.09	NS
Total 80 min. amylase/kg. (U./kg.)	28.4 (13.5)	23.8 (10.0)	0.8	NS	27.14 (11.04)	24.3 (10.2)	0.6	NS

In parenthesis Standard Deviation of the mean

Another finding that should be considered when evaluating the differences related to sex is that both in man[11] and dog[10] there is no correlation between body weight and pancreas weight. In humans, according to Schaefer,[11] the difference of the average pancreatic glands weights between males and females is only 5 gm. (85 for women, 90 for men). From this latter finding, it is obvious that when secretin is administered to two subjects of different body weight, the heavier one receives a progressively greater amount of the hormone relative to the size of his pancreas, in direct proportion to the magnitude of the body weight difference between both individuals. This reasoning could explain our sex-linked different results with Boots secretin (Table V) but this postulation is not substantiated either by our Vitrum series results (Table IV) or by the above mentioned Hansky, et al[10] findings. At present it seems that one has to admit that the sex-related difference in results is due to a greater sensitivity to secretin of the "pancreon's" centroacinar-ductal segment in men than in women. The basis of this peculiarity could be connected with a different interaction at "pancreon" level of secretin with the sex hormones and/or the basal intrapancreatic autonomic nervous tone.[12,13]

Confirming the results of the Dreiling school[3] and in contradistinction to what is observed in the stomach,[14] the exocrine pancreas secretion is influenced little by the age of the subject.

Unexpectedly, the secretin tests results were not influenced by the previous sorbitol intraduodenal infusion. The 30-minute lapse between both tests [2,6] seems to allow the extinction of the probable potentiating influence on the pancreocites of the sorbitol-evoked CCK released from the "pancreon's" trigger zone.[1,2]

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The Pancreas

A Correlation of Function and Structure

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Fifty-two patients with or without pancreatic disease were studied with both secretin test and endoscopic retrograde pancreatography. Pancreatic histopathology was obtained by exploratory laparotomy in half of these patients. The following conclusions were reached: 1. Secretory tests are the most sensitive indicators of chronic pancreatitis, although not all cases of chronic pancreatitis will be discovered by this test. 2. When secretory tests show low volume output, pancreatography is crucial in differentiating between malignant ductal obstruction or pancreatic replacement by fibrosis or atrophy. 3. Histologic correlation with ductular structure and/or secretin function is frequently discordant. 4. The secretin test and pancreatogram measure different parameters and the use of both these complementary studies will lead to increased diagnostic accuracy and better understanding of pancreatic pathophysiology.

Endoscopic retrograde pancreatography has recently been introduced as a new modality in the study of pancreatic diseases.[1-3] The endoscopic pancreatogram provides information about the patency and configuration of the main pancreatic duct but little or no information concerning the smaller branches and acini of the gland. The value of this new procedure as a parameter of pancreatic pathology should be assessed in relation to established indices of pancreatic dysfunction such as the secretin test and the pancreatic histology. The purpose of this present study is to compare the diagnostic value of endoscopic pancreatography with secretin tests obtained from the same patients. Pancreatic tissue was obtained at surgery from several patients and correlation of histology with the results of the secretin test and endoscopic pancreatography was possible.[4]

Materials and Methods

Fifty-two patients referred to The Mount Sinai Hospital between January, 1973 and April, 1975 for investigation of suspected pancreatic disease had both a secretin test and an endoscopic retrograde pancreatogram (ERP), performed in that order within one week's time. All patients were examined clinically and a complete gastroenterological investigation was undertaken to establish the diagnosis. Exploratory laparotomy was performed in 26 patients, and in most of these patients tissue was available for histologic study of the pancreas. Pancreatic function was measured by both a standard and augmented

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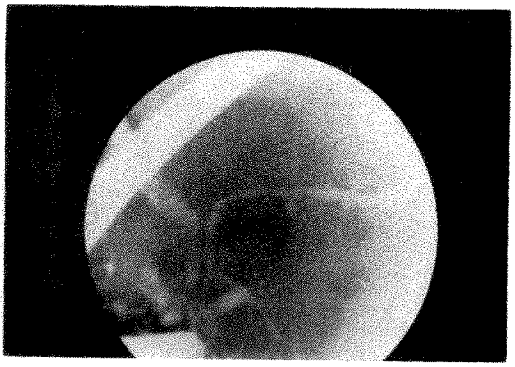

Fig. 1—Slight beading of the pancreatic duct indicative of mild pancreatitis. Note the dilatation of secondary radicals in the body of the pancreas.

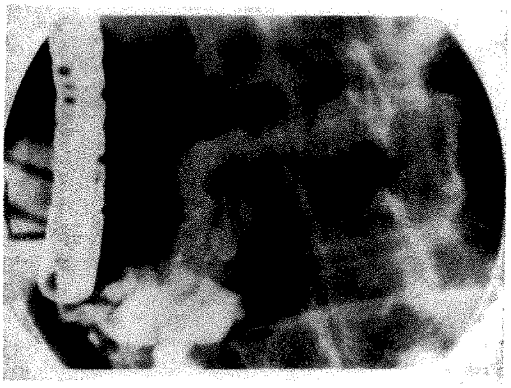

Fig. 2—Marked ductal dilatation and stricture in the mid pancreas indicative of chronic pancreatitis.

secretin test.[5] For this study, only results obtained by the standard secretin test were used for correlative purposes.

In all patients the secretin test results may be divided into four categories: 1. Normal in both volume and bicarbonate concentration. 2. Low volume and low bicarbonate concentration, indicative of chronic pancreatitis. 3. High volume associated with hypersecretion. 4. Low volume and normal bicarbonate concentration, suggestive of ductular obstruction due to carcinoma or severe chronic pancreatitis with glandular fibrosis.

Endoscopic pancreatography was performed with the Olympus JF-B flexible fiberoptic endoscope. The results of ERP may be interpreted in three separate categories: 1. Normal pancreatic duct. 2. Beading (Fig. 1) or ductular dilation and strictures (Fig. 2) suggesting chronic pancreatitis. 3. Obstruction suggesting carcinoma (Fig. 3).

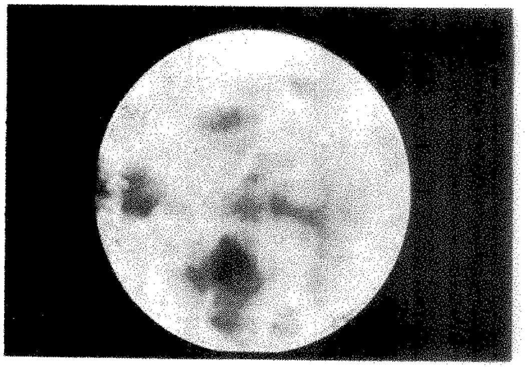

Fig. 3—Obstruction of the pancreatic duct just to the left of the spine. This tapered, completely obstructed duct is indicative of carcinoma.

TABLE I

SECRETIN TEST—NORMAL (21 PATIENTS)

Final diagnosis	Total	Pancreatogram	
		Abnormal	Normal
No pancreatic disease	14	0	14
Chronic pancreatitis (proven with histology)	4	4	0
Acute pancreatitis	2	0	2
Recurrent acute pancreatitis	1	0	1

The histologic appearance of the pancreas was evaluated in terms of interlobular fibrosis, acinar atrophy and ductular dilation. The histopathology was divided into four categories including: 1. Plus-minus—indicating minimal disease. 2. One-plus—slight but definite evidence of pathology.

TABLE II

SECRETIN TEST—CHRONIC PANCREATITIS (21 PATIENTS)

Final diagnosis	Total	Pancreatogram	
		Abnormal	Normal
Chronic pancreatitis (all with histology)	17	12	5
Presumably chronic pancreatitis (no histology)	4	0	4

TABLE III

SECRETIN TEST—HYPERSECRETION (4 PATIENTS)

Final diagnosis	Pancreatogram	
	Abnormal	Normal
* Chronic pancreatitis	0	1
Alcoholism	0	1
* Chronic hepatitis	0	1
* Primary biliary cirrhosis	0	1

* Diagnosis proven by histology

TABLE IV

SECRETIN TEST—LOW VOLUME (6 PATIENTS)

Final diagnosis (all with histology)	Pancreatogram	
	Abnormal	Normal
Cancer	2	0
Partial resection	1	0
Chronic pancreatitis	0	1
Normal pancreas Metastatic carcinoma to liver Hypernephroma	0	2

3. Two-plus—moderate pathology. 4. Three-plus—severe pathology.

RESULTS

Group 1:—Secretin test normal (21 patients)—Table I. Fourteen patients had no clinical evidence consistent with pancreatic disease and with a normal secretin test and a normal ERP were deemed to be free of pancreatic disease. Two patients had acute pancreatitis and one had recurrent acute pancreatitis; all three had normal ERP, consistent with the acute nature of their disease. Four patients had beading of the pancreatic duct on ERP and at exploratory laparotomy chronic pancreatitis was demonstrated histologically in all of these patients.

The finding of a normal secretin test and an abnormal duct on ERP indicates that in some cases pancreatic inflammatory responses may disproportionately affect the anatomy of the ductal system, or that the parenchyma, although damaged, has enough reserve to respond normally to a secretin stimulus.

Group 2:—Secretin test suggesting chronic pancreatitis (21 patients)—Table II. Seventeen patients had histologic examination of pancreatic tissues and all showed chronic pancreatitis. Twelve of these 17 patients had an abnormal pancreatogram and five had normal ERP. An additional four patients had abnormal secretin tests and were termed "presumably chronic pancreatitis" since there was no histological proof of that diagnosis: the pancreatograms of all four of these patients were normal.

Nine of 21 patients with secretin tests showing chronic pancreatitis revealed normal ERP. Correlation with histology revealed that marked parenchymal changes may occur in the absence of any narrowing or deformity in the ductal system.

Group 3:—Secretin test showing hypersecretion (four patients)—Table III.

TABLE V

CHRONIC PANCREATITIS—CORRELATION OF HISTOLOGY, SECRETIN AND ENDOSCOPIC PANCREATOGRAM

Patient	Interlob. fibrosis	Acinar atrophy	Ductular dilatation (small duct)	Secretin			Pancreatogram
				HCO_3 mEq./l. NML 90	Vol. ml./kg. NML 2.0-4.4	Diagnosis	
G. Pet	±	±	−	45	3.0	C.P.	Normal
I. Ber	+	+	+	92	1.0	C.P.	Slightly irregular (C.P.)
A. Cai	++	++	+	95	2.9	Normal	Pseudocyst
Anay	+++	+++	±	68	3.5	C.P.	Dilated duct and strictures
R. Ros	+++	+++	+	36	2.9	C.P.	Dilated and shortened (Postop.)
Lewi	+++	+++	++	56	0.7	C.P.	NML but short duct (Postop.)
Mose	+++	+++	++	50	2.4	C.P.	Dilated duct and strictures

None of these four patients had evidence of abnormality on pancreatogram. The diagnoses were "early alcoholic pancreatitis", "chronic hepatitis", "primary biliary cirrhosis" and "chronic pancreatitis". The last three patients had histological confirmation of the diagnosis.

There is no identifiable ductal abnormality associated with pancreatic hypersecretory states.

Group 4:—Secretin test showing low volume (six patients)—Table IV. Half of the patients in this group had an abnormal pancreatogram, with obstruction in two patients due to carcinoma and a shortened gland in one patient following partial resection of the pancreas. In the three cases with normal ERP, laparotomy revealed one patient had chronic pancreatitis with glandular fibrosis accounting for the low volume and the other two had a normal pancreas without evidence of significant disease.

Although low secretory volume may be secondary to ductal obstruction from carcinoma or fibrosis of the pancreas due to pancreatitis, it may occasionally be associated with a normal gland.

The correlation of histology with the secretin test and endoscopic pancreatography is shown in Table V. The first patient (G. Pet) had a normal ERP with marked abnormality of secretion but only mild histological evidence of pancreatic disease. The second patient (I. Ber) demonstrates a positive correlation of all three parameters, while the third patient (A. Cai) reveals evidence of a normal secretory capacity with a pseudocyst on pancreatogram and mild pancreatic fibrosis and acinar atrophy. The last four patients demonstrated a positive correlation for all three parameters, with one patient (Lewi) having a short pancreatic duct secondary to previous partial pancreatectomy.

The functional secretory capacity of the pancreas may not correlate well with the histologic structure of the gland.

COMMENT

Fifty-two patients with and without pancreatic disease were studied with a combination of the secretin test and endoscopic retrograde pancreatography. Pancreatic histology and pancreatic pathology were ascertained by exploratory laparotomy in half of these patients. Analysis of data permits the following four conclusions:

1. Secretory tests remain the most sensitive indicator of chronic pancreatitis, although not all cases of chronic pancreatitis will have sufficient diminution of secretory capacity to permit discovery by the secretin test. It is impossible to ascertain whether any patients actually had chronic pancreatitis but were not discovered by the combination of the secretin test and ERP, since only patients with definite abnormalities on these studies were submitted to surgery. The data in Table VI obtained from histological evidence of 24 patients operated on with chronic pancreatitis demonstrate that the secretin test missed four (16%) patients with chronic pancreatitis, where the ERP missed seven (30%) patients. Analysis of the data from patients in Group 1, with four abnormal pancreatograms in 21 patients with normal secretin tests reveal that the pancreatic parenchyma, although damaged by chronic pancreatitis, may have enough reserve to respond normally to a secretin stimulus, even though the ductal system may show some abnormalities. Conversely, correlation with histology showed that, especially in patients in Group 2, marked fibrosis and acinar atrophy may occur in the absence of any deformity of the ductal system. These patients will reveal pancreatic insufficiency on secretory testing, with a normal ERP. Since the secretin test and pancreatogram

TABLE VI

CHRONIC PANCREATITIS
(24 PATIENTS WITH HISTOLOGY)

Pancreatogram	Secretin	
	Normal	Abnormal
Normal	0	7
Abnormal	4	13

measure different parameters, increased diagnostic accuracy requires the use of both these complementary studies in the evaluation of patients with chronic pancreatitis. These conclusions agree with the views of Nakano, et al[6] and Cotton, et al[7] in their studies of the correlations of these tests.

2. Hypersecretory states of the pancreas[8] present a nonhomogeneous group of patients, none of whom are expected to have pancreatic ductal abnormalities and none were found in this study.

3. Patients with low volume may have a diminished pancreatic secretory flow due either to carcinoma of the head or body of the pancreas with ductal obstruction or due to significant replacement of pancreatic tissue by fibrosis secondary to chronic pancreatitis. Incomplete collection of pancreatic juice may also account for inclusion of some patients in this category. The correct diagnosis in this group of patients can best be made by ERP. The finding of a complete obstruction of the pancreatic duct renders an unequivocal diagnosis of carcinoma, and this finding may be readily distinguished from those instances of advanced pancreatitis with fibrotic nonfunctioning pancreatic gland.

4. The histologic changes of pancreatic fibrosis and acinar atrophy may not be completely parallel with the findings of secretory testing and ERP since structure and function vary. Chronic pancreatitis may affect parenchyma much more than the major pancreatic ducts and produce a normal ERP with rather marked secretory dysfunction, or the pancreatic parenchymal damage may be spotty, and give rise to an apparently mild histologic pancreatitis while the secretory capacity may be severely compromised.

Since the secretin test and pancreatogram measure different parameters, increased diagnostic accuracy and better understanding of pathophysiology requires the use of both these complementary studies in the diagnosis and treatment of the pancreas.

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Intrasplenic Pancreatic Pseudocyst Complicating Severe Acute Pancreatitis

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Since 13 cases of intrasplenic pancreatic pseudocysts have been previously described in the world literature, an additional case is reported. The mechanisms for the development of this lesion are: 1. direct extension of the pancreatic cyst into the splenic hilum; 2. digestive effects of pancreatic enzymes on splenic vasculature and parenchyma; 3. pancreatitis occurring in ectopic intrasplenic pancreatic tissue and 4. liquefaction of splenic infarcts secondary to thrombosis of the splenic vessels. Criteria for diagnosis and current available diagnostic methods are discussed. Early surgical intervention with splenectomy and possibly caudal pancreatectomy, is advocated.

While infection, perforation and hemorrhage are well recognized complications of pancreatic pseudocysts,[1] only 13 cases of intrasplenic dissection of pseudocysts have been reported in the world literature.[2-8] It is therefore felt that a report of an additional case would be of interest.

Case Report

S. S., a 27-year old black, male, was admitted to Harrison S. Martland Medical Center, complaining of upper abdominal pain, malaise and shortness of breath of four weeks' duration. He was a chronic alcoholic, consuming one quart of whiskey daily for the past eight years. The pain radiated to the back and to both flanks.

On admission the blood pressure was 110/80 mm. Hg., temperature 39° C, and pulse rate 100/min. Relevant physical findings were confined to the chest and abdomen. Examination of the chest revealed decreased breath sounds and dullness to percussion over the left lower lung field. The abdomen was moderately distended and tender. A poorly defined mass was palpated in the epigastrium.

The abnormal laboratory values were as follows: hemoglobin, 10.6 gm.%; hematocrit, 33%; white blood cell count 15,700/cu. mm.; serum amylase 560 Conway units (normal 60-160 units).

Since the chest roentgenogram showed a left-sided pleural effusion, thoracentesis was performed, yielding 170 ml. of straw colored fluid. The fluid contained 5.0 gm.% protein; 18,000 red blood cells/cu. mm.;

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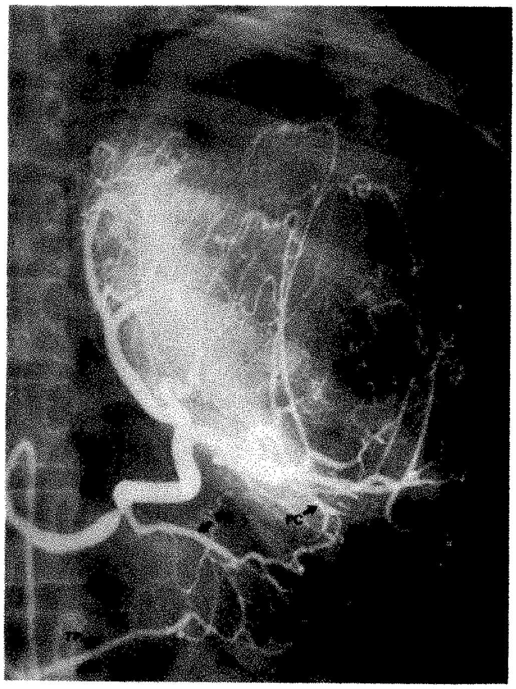

Fig. 1—Arterial phase of supraselective splenic arteriogram. Marked stretching and displacement of the splenic arterial branches which extend only to the medial half of the spleen is present. The pancreatic arterial supply is well demonstrated; pancreatic magna (PC) and pancreatic caudate vessels communicate via multiple branches to fill the transverse pancreatic artery (TP).

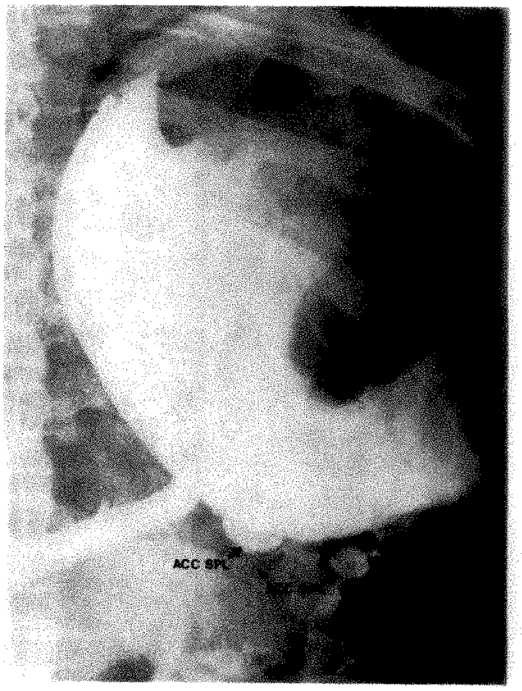

Fig. 2—The splenogram phase shows a large lateral defect, which separates the visualized thickened splenic capsule (arrows) from the irregular contour of the spleen medially. Differentiation between a subcapsular hematoma and a pseudocyst cannot be made. Note the accessory spleen near the lower pole. The tail and body of the pancreas is intact and the splenic vein courses along the upper border of the pancreas.

200 white blood cells/cu. mm. and 400 Conway units of amylase.

Four days after admission, the patient again became dyspneic and the hematocrit fell to 26%. He was placed on nasogastric suction, intravenous fluids and antibiotic therapy consisting of clindamycin and ampicillin. On the seventh hospital day, a closed tube thoracostomy was performed, due to the recrudescence of the left pleural effusion and 500 ml. of straw colored fluid was recovered.

Since his clinical condition failed to improve, it was decided to perform an exploratory laparotomy, with the tenative diagnosis of an infected pancreatic pseudocyst. At celiotomy, a large, thin walled cyst, involving the distal half of the pancreas and in juxtaposition to the stomach, was encountered. Because of the immaturity of the cyst wall, external drainage was performed. Specimens of the cyst fluid were cultured and a beta hemolytic streptococcus was isolated, susceptible to both ampicillin and clindamycin. The amylase content of the cyst fluid was 2,700 Conway units.

Postoperatively, he was placed on central venous hyperalimentation and because of respiratory complications, a tracheostomy was performed. He subsequently slowly improved over the next two weeks.

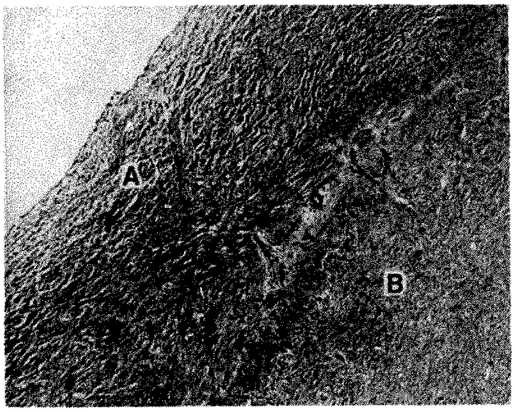

Fig. 3—Photomicrograph of the spleen, demonstrating a thickened cyst wall (A) and splenic parenchyma (B) (original magnification x120).

An upper gastrointestinal series was performed which demonstrated extrinsic pressure on the stomach. A selective celiac arteriogram, carried out 21 days postoperatively, revealed an avascular area of the spleen (Figs. 1 and 2). This was interpreted to represent either a splenic hematoma or an intrasplenic pseudocyst. The abdomen was re-explored through a left subcostal incision at about six weeks following the initial operation. The spleen was found to be moderately enlarged and contained a cystic mass which was inadvertently ruptured during splenectomy. The cyst fluid was straw colored and had an amylase content of 733 Conway units.

Histopathological examination of the spleen was unremarkable and the cyst wall showed a nonepithelial lining with chronic inflammatory changes (Fig. 3). The patient pursued an uneventful postoperative course and was discharged eight days later. He was readmitted after two years with acute, alcoholic pancreatitis that responded to conservative therapy.

COMMENT

According to Bolivar and Lempke,[2] these cysts, in order to be considered as intrasplenic, should be completely surrounded by splenic capsule or parenchyma. These authors also stipulate that one of the following criteria should be utilized for confirmation of the pancreatic origin of intrasplenic cysts: 1. the presence of pancreatic tissue in or adjacent to the wall of the cyst; 2. an amylase level in the cyst fluid higher than that in the serum; 3. gross or microscopic evidence of pancreatitis without a history of recent trauma and no evidence of other primary or secondary splenic disease.

The four possible mechanisms by which intrasplenic pancreatic cysts develop are: 1. direct extension of pancreatic cysts into the spleen through the splenic hilum; 2. digestive effects of pancreatic enzymes upon the splenic vasculature and parenchyma; 3. pancreatitis occurring in ectopic intrasplenic pancreatic tissue and 4. liquefaction of splenic infarcts secondary to thrombosis of the splenic vessels.[2] The embryologic association of the spleen and the pancreas and the close anatomic relationship of these two organs, provide an adequate explanation for these mechanisms. During development, the spleen and the caudal pancreas are situated close to each other in the dorsal mesogastrium. Therefore, ectopic splenic tissue may be found in close proximity to the pancreas and ectopic pancreatic tissue may be trapped between the aggregates of mesoderm that fuse to form the spleen. Heterotopic pancreatic tissue may be complicated by the development of acute pancreatitis[9] and pancreatic pseudocyst.[7]

Anatomically, the splenic capsule is continuous with the peritoneum that encloses the splenic vessels and covers the anterior surface of the pancreas. This provides an easy route for exudative pancreatic fluid to enter the hilum of the spleen. Pancreatic pseudocysts are usually formed within the lesser sac. The dissection of enzyme-rich exudate or pancreatic juice through anatomic planes may result in cystic collections extending from the neighborhood of the pancreas to remote sites such as the neck[10] and the scrotum.[11]

In the case reported here, the decision to perform splenectomy was based upon angiographic findings that suggested the presence of either a splenic hematoma or intrasplenic dissection of a pancreatic pseudocyst. The diagnosis of the latter condition was confirmed by the high amylase content of the cystic fluid, by recent evidence of acute pancreatitis noted at the time the pseudocyst was initially drained, and by the absence of a true epithelial lining of the cyst wall upon microscopic examination of the splenic cyst. The arteriogram confirmed the patency of the splenic vessels and excluded the possibility of splenic infarction on an avascular basis.

The most plausible explanation for the development of the intrasplenic pseudocyst in our case, is that fluid from the original pseudocyst dissected through anatomic planes through the splenic hilum into the parenchyma of the spleen.

Traditionally, the diagnosis of pancreatic pseudocyst has been based on the clinical features of the case and barium contrast studies of the gastrointestinal tract. Such masses may, however, be due to noncystic, inflammatory processes that may regress over a period of time.[12]

The problem of differentiating cystic from solid lesions in the pancreas is greatly simplified by diagnostic ultrasound echograms of the upper abdomen. Bradley, Gonzalez and Clements[13] have substantiated the diagnostic value of this safe and noninvasive technic. They employed diagnostic ultrasound in evaluation of 19 patients with a clinical diagnostic impression of pancreatic pseudocyst. In 10 of these patients, pseudocysts were predicted by ultrasound and confirmed at laparotomy. In nine cases, a diagnosis of phlegmonous pancreatitis was suggested by ultrasound examination and was correct in eight, with only one false negative report. They advised that ultrasound should be employed in patients with acute pancreatitis when any one of the following conditions is recognized: 1. palpable evidence of an abdominal mass; 2. a lack of clinical improvement; 3. persistent elevation of serum or urinary amylase levels; 4. roentgenographic evidence of gastrointestinal displacement or 5. the development of intra-abdominal sepsis.

Although this diagnostic modality was not employed in our case due to its unavailability at the time the patient was treated, it would have been useful in sequentially following the patient during his hospital course and might have aided in early detection of the intrasplenic dissection.

The adjunctive use of duodenal endoscopy with retrograde pancreatography may delineate an intrasplenic dissection if communication between the pancreas and the intrasplenic cyst is present either directly or via a peripancreatic exudative accumulation.[12] This test may also assist in the detection of pancreatic ascites.

While splenic scans and ultrasound are helpful screening procedures, selective angiography will provide more exact information on the status of the splenic vasculature.[8] Cystic conditions will appear as avascular areas with the displaced splenic vessels splayed out over the mass. Splenic neoplasms may be differentiated from cysts by the presence of a "tumor blush" and dilated neovasculature.

The consequences of intrasplenic dissection may be life-threatening and include splenic rupture, erosion of the splenic vessels with resultant hemorrhage, or thrombosis of the splenic vessels with infarction of the spleen.[8] Splenic rupture occurring in association with acute pancreatitis may be due to adhesions between the spleen and contiguous structures, to trauma, or to enzymatic digestion of the splenic parenchyma.[14-16]

The conventional therapy in the early stages of pancreatic pseudocysts consists of supportive medical management with nasogastric suction and intravenous fluids. Prior to the maturation of the cyst wall, surgical intervention is more compelling when other acute abdominal diseases are suspected or when surgically treatable complications develop. One of these complications is intrasplenic dissection. We concur with Warshaw and associates[8] who emphasize the urgency of splenectomy and possibly caudal pancreatectomy due to the potentially lethal nature of this lesion.

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The Effects of Intravenous Sodium Octanoate on the Rhesus Monkey

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Infusions of sodium octanoate in doses of 5 mM./kg. over a period of 20 minutes produced a clinical and electroencephalographic syndrome resembling hepatic encephalopathy in five Rhesus monkeys. These and other animal experiments, coupled with the finding of elevated serum levels of octanoate in cirrhotic patients, suggest the possibility of this agent's playing a role in the pathogenesis of hepatic encephalopathy.

Elevation of serum levels of octanoate in hepatic encephalopathy have been noted by several investigators.[1-6] Linscheer, et al[3, 4] has demonstrated that both mild and severe cirrhotic patients have higher serum levels of octanoic acid than do controls and that cirrhotic patients develop abnormally high levels of serum octanoate after the rectal administration of an octanoate test solution of medium chain triglycerides. Various degrees of hepatic encephalopathy developed in four of Linscheer's cirrhotic patients while they were receiving therapy with medium chain triglycerides. In addition, serum octanoate has been reported to induce reversible coma in various species of experimental animals alone or when administered with ammonium salts.[7-10]

Recent work by the authors[6] has utilized a new methodology for measuring serum octanoate, involving extraction with alkaline ethanol and steam distillation followed by gas-liquid chromatography. The results of this method were confirmed by mass spectrophotometry. Serum fasting levels of serum octanoate were determined in 24 controls and 79 patients with cirrhosis; of the latter, 50 had varying degrees of hepatic encephalopathy. Arterial and venous concentrations of octanoate were significantly higher in patients with coma than in those not in coma. The arterial concentration was significantly higher than the

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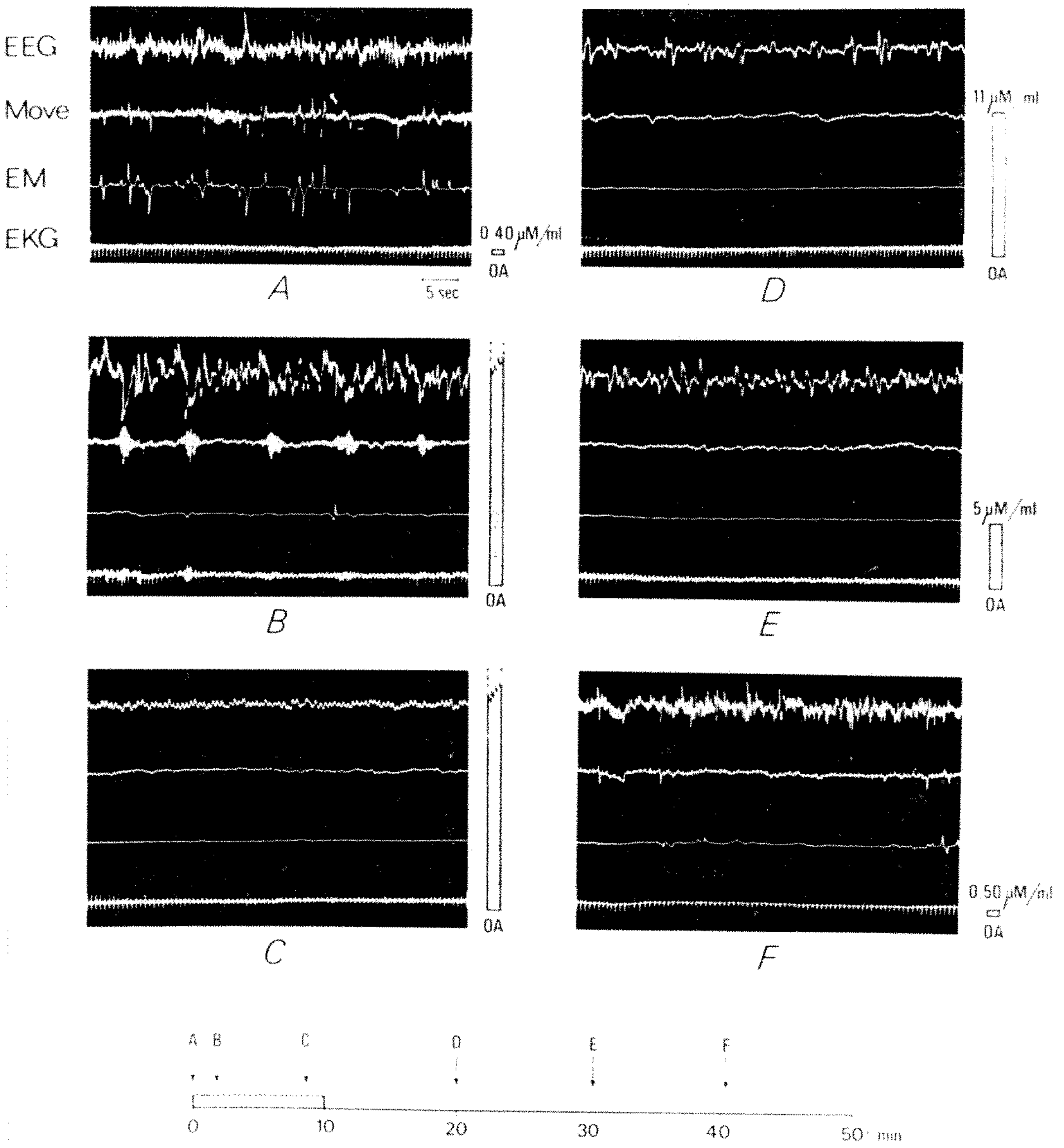

Fig. 1—Polygraphic study in *Macaca mulatta* in which reversible coma was induced by the intravenous injection of 5mM./kg. of sodium octanoate over a period of 10 minutes.

EEG = electroencephalogram
Move = neck muscle activity
EM = eye movements
EKG = used for timing

A. Normal; B. Myoclonic jerks; C. Coma and muscle hypotonia without eye movements; D. Trephasic waves; E. Delta waves; F. Return to normal.

Levels of octanoic acid are shown on abscissa. Ordinate shows time relationship of each recording following octanoate injection.

venous. Data obtained utilizing 14C-palmitate labeled at different carbons, suggested that incomplete oxidation of palmitate in the cirrhotic patients was probably the origin of the blood octanoate.[11]

Sodium octanoate-induced coma has been studied in the cat, rat and rabbit.[7-10] This paper reports our experience with sodium octanoate-induced coma in a primate.

MATERIAL AND METHODS

Five adult (4-5 kg.) female Rhesus monkeys (*Macaca mulatta*) were studied. A cranial platform was fixed above the scalp and recording wires for EEG and extraocular and posterior neck muscle were soldered to pin connectors cemented to the platform. Silicone rubber cannulas were implanted in the right atrium and the left jugular vein and threaded under the skin of the neck to the cranial platform. The monkeys, previously conditioned to a primate restraining chair for several weeks, received sodium octanoate (0.625 M in isoosmotic NaCl adjusted to a pH of 7.35 with HCl) intravenously over a period of 10 minutes.

RESULTS

Two minutes after the beginning of the perfusion, muscular hypotony developed in all animals followed by the appearance of sleep characterized by slow, high amplitude encephalographic waves (Fig. 1A). Slow (12/min.) myoclonic movements then developed involving the entire body but with predominant activity in the extremities (Fig. 1B). This was followed by a period of approximately 10 minutes in which there was almost complete muscle atony as in paradoxical sleep without eye movement (Fig. 1C). The EEG at this time registered 1.5 c/s rhythmical activity. This phase was followed by a period of nonrhythmical EEG paroxysms occurring with bi- or triphasic wave patterns (Fig. 1D). Neck muscle activity slowly reappeared (Fig. 1E), followed by eye movement and delta waves. The polygraph returned to normal 40 minutes after the beginning of the infusion, at which time the EEG became desynchronized (Fig. 1F).

COMMENT

Elevation of serum levels of octanoate in cirrhosis of the liver and hepatic encephalopathy seems well established.[1-5] The authors have performed 190 octanoate determinations in 2.4 control subjects and in 79 patients with cirrhosis of whom 50 were in some stage of hepatic encephalopathy.[6] Coma was graded from 0 to 5 according to the classification of Sherlock.[12] Grade 0 corresponds to a cirrhotic patient with a normal mental and neurological state.

Arterial and venous concentrations were significantly higher in cirrhotic patients than in controls ($P < .01$). Both arterial and venous concentrations were significantly higher in cirrhotic patients with coma than in those not in coma ($P < .05$). Normal venous concentrations of octanoate are considered to be less than < 5 μEq./l. with a mean value of 1.5 μEq./l. Levels in cirrhotic patients were frequently above 10 μEq./l. with top levels of 18 μEq./l. In comatose patients there appeared to be a correlation between blood octanoate and ammonia levels.[6]

Elevations of serum octanoate have been considered to be due to either 1. incomplete oxidation of longer chain fatty acids or, 2. incomplete build up and elongation of shorter chain fatty acids. Recent studies[11] utilizing radioactively labeled palmitate indicate that incomplete oxidation of long chain fatty acids such as palmitate probably accounts for the octanoate elevations.

It remains uncertain as to whether elevated serum octanoate is a causative factor of hepatic encephalopathy or an incidental finding resulting from serious hepatic disease. The occurrence of hepatic encephalopathy in cirrhotic patients receiving medium chain triglycerides and its apparent production by infusion of sodium octanoate in experimental animals suggests an etiological role. It must be emphasized that the "coma dose" of sodium octanoate in the present experiment produced serum concentrations many times those measured in comatose cirrhotic patients. In addition, the mechanism of octanoate-induced encephalopathy remains to be elucidated. Normal concentrations of adenosine triphosphate and phosphocreatinine have been found in both the cerebral cortex and brain stem of rats at the beginning of and during octanoate-induced coma. Energy utilization rates in both brain areas were found to be normal at the inception of coma.[13]

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Clinical Vignette

Chronic Active Hepatitis and Ulcerative Colitis Associated with Eosinophilia, Nonthrombocytopenic Hypergammaglobulinemic Purpura and Serologic Abnormalities

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A patient with chronic active hepatitis (CAH) and ulcerative colitis (UC) associated with eosinophilia, nonthrombocytopenic hypergammaglobulinemic purpura and serologic abnormalities is presented. Abnormal liver function, gastrointestinal and systemic symptoms as well as the associated epiphenomena responded dramatically to oral corticosteroid therapy. The remission was maintained during an eight month follow-up period with low dose prednisone therapy.

INTRODUCTION

CAH and UC are both felt to involve immunological derangements, and the concurrence of the two diseases is well known.[1] Many immunological abnormalities have been reported with CAH[2] and UC[3] but their exact role in the pathogenesis of the diseases is unknown, although they may be responsible for the production of some of their extrahepatic and extracolonic manifestations. These epiphenomena may antedate the onset of the CAH and UC, or occur anytime during the clinical course. Indeed, they may overshadow the underlying pathology.

This report concerns a patient with long-standing CAH and UC who presented with the uncommon combination of eosinophilia, nonthrombocytopenic hypergammaglobulinemic purpura and serologic abnormalities. All of these epiphenomena responded dramatically to corticosteroid therapy.

CASE REPORT

A 44-year old West Indian, black, female was admitted to The Mount Sinai Hospital on 15 January 1976 with a one-month history of nausea, diarrhea and intermittent abdominal pain accompanied by low grade fever, night sweats, weight loss, myalgia and migratory arthralgia.

In February, 1962, evaluation for bloody diarrhea yielded a diagnosis of ulcerative colitis on the basis of barium x-ray studies and sigmoidoscopy with biopsy. Symptoms were controlled with a short course of high dose prednisone therapy. In October, 1962 the patient was readmitted with *pyoderma gangrenosum* of the left leg which necessitated an above the knee amputation. A liver biopsy performed to explain an elevation of the serum transaminase activity was unremarkable. The liver biopsy was repeated, however,

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in 1963. The specimen showed chronic active hepatitis with lobular involvement. At that time, the patient had a persistent eosinophilia of 4-8% and a white cell count of 6-10,000 cells/cu. mm. Numerous stool specimens were negative for ova and parasites and two skin and muscle biopsies were unremarkable.

Subsequently she experienced several recurrent episodes of colitis which were controlled with prednisone and Azulfidine. In 1965, the patient underwent an exploratory laparotomy to rule out carcinoma in a large polypoid lesion found on barium enema. Postoperative thrombophlebitis developed and recurrent pulmonary emboli necessitated an inferior vena caval ligation. The patient was transfused with four units of blood. Between 1973 and 1975 the patient had three episodes of uveitis. In February, 1974 serum alkaline phosphatase activity was 124 mU./ml.; total bilirubin, .5 mg./100 ml.; SGPT, 128 mU./ml.; SGOT, 163 mU./ml.; total protein, 9.3 gm./100 ml. and gamma globulin, 5.8 gm./100 ml. The white blood cell count was 9,200/cu. mm. with 63% neutrophils, 18% eosinophils and 19% lymphocytes. The patient was not taking any medications at that time.

She was lost to medical follow-up until one month prior to this admission when she developed nausea, brown watery diarrhea, intermittent crampy abdominal pain, low grade fever, night sweats, weight loss, myalgia and migratory arthralgia. She experienced some relief of diarrhea with Azulfidine, which she terminated two weeks prior to admission. The patient took no other medications and denied alcohol intake. Ten days prior to admission the serum alkaline phosphatase activity was 198 mU./ml.; total bilirubin, .7 mg./100 ml.; SGPT, 196 mU./ml.; SGPT, 186 mU./ml.; total protein, 10.1 gm./100 ml.; globulin, 5.8 gm./100 ml. and gamma globulin, 3.5 gm./100 ml. The erythrocyte sedimentation rate was 71 mm./hr. and the hepatitis B surface antigen and antibody were negative. The hematocrit was 35.5% with a white blood cell count of 18,900/cu. mm. with 46% neutrophils, 38% eosinophils, 14% lymphocytes and 2% monocytes.

On admission, examination of the abdomen revealed a firm nontender nonnodular liver with a span of 20 cm. in the mid clavicular line and palpable spleen tip. Rectal examination revealed a nontender irregular polypoid mass. The stool had a trace of blood. Many nontender purpuric and urticarial lesions, 1-2 cm. in diameter with discrete borders, were found on the calves and thighs. There were no muscle tenderness or weakness or joint abnormalities.

Initial laboratory data included an erythrocyte sedimentation rate of 115 mm./hr.; hemoglobin, 10.9 gm.%, white blood cell count, 44,100/cu. mm. with 18% neutrophils, 2% bands, 69% eosinophils, 3% basophils, 7% lymphocytes and 1% monocytes and platelet count 463,000/cu. mm. The peripheral blood smear showed microcytic hypochromic red blood cells and eosinophilia without immature forms. The serum alkaline phosphatase activity was 369 mU./ml.; total bilirubin, 3.6 mg./100 ml.; direct bilirubin, 2.6 mg./100 ml.; SGPT, 246 mU./ml.; SGPT, 619 mU./l.; total protein, 11.8 gm./100 ml. and albumin 2.95 gm./100 ml. Immunoelectrophoresis showed a diffuse hypergammaglobulinemia with an Ig-G of 4,700 mg./100 ml.; Ig-A of 820 mg./100 ml. Ig-M of 1,020 mg./100 ml. Urine analysis, chest x-ray and electrocardiogram were unremarkable.

Bone marrow aspiration revealed a hypercellular marrow with marked eosinophilia, which made up 30% of the total nucleated cells. The myeloid series showed no maturation defect and iron stores were

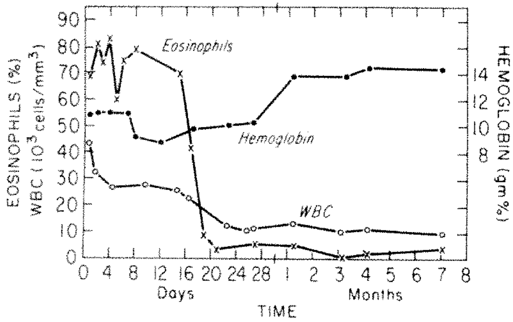

Fig. 1—Normalization of the complete blood count following prednisone administration.

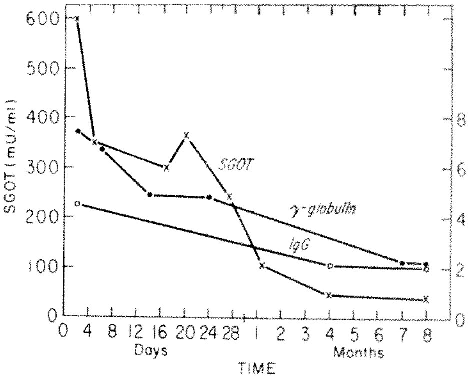

Fig. 2—Normalization of the serum immunoglobins and SGOT following prednisone administration.

absent. First and second strength intradermal purified protein derivative testing was negative. Numerous stool specimens were negative for ova and parasites. Cold agglutinins and cryoglobulins were absent. Antinuclear antibodies were absent and the *lupus* preparation was negative. Latex fixation was positive in a titer of 1 to 160. Hepatitis B surface antigen and antibody, mitochondrial and smooth muscle antibodies were absent. Trichinella antibodies were absent by counterimmunoelectrophoresis. The Coombs' test was negative. Blood and urine cultures showed no growth. The VDRL was weakly positive in a titer of 1 to 1. The initial prothrombin time (PT) was 24 seconds with a control of 12.8 seconds. The PT did not respond to parenteral Vitamin K. No circulating anticoagulants were present.

The patient experienced persistent diarrhea accompanied by diffuse abdominal pain with the passage of five to eight unformed stools per day which remained guaiac positive. Nonspecific myalgia and arthralgia persisted. Sigmoidoscopy to 25 cm. revealed a granular, friable and bleeding mucosa with pseudopolyps along the entire rectosigmoid. Barium enema demonstrated universal colitis with multiple polypoid filling defects in the sigmoid, descending colon and proximal ascending colon. Upper gastrointestinal series showed thick nodular folds with increased secretions in a dilated terminal ileum, consistent with "backwash ileitis". Liver-spleen scan indicated enlargement of both organs with increased bone marrow uptake. Biopsy of the skin lesions revealed mild nonspecific vasculitis with acute inflammation surrounding the vessels in the dermis and subcutaneous fat. On the 17th hospital day the patient was started on 60 mg. of prednisone daily. In the course of the next two weeks her arthralgias and myalgias decreased. Diarrhea diminished to two to three semi-formed stools per day. The eosinophilia promptly responded to prednisone administration with normalization of the complete blood count (Fig. 1). The liver function tests and the gamma globulin level also returned toward normal (Fig. 2). Repeat bone marrow aspiration revealed 7% eosinophils. The patient was discharged on the 27th hospital day on prednisone 60 mg. daily.

As an outpatient, the amount of prednisone received was reduced over eight weeks to 20 mg. daily. During this period the patient's gastrointestinal and joint complaints abated. The purpuric skin lesions began to resolve. Two months after discharge her coagulation profile returned to normal and she was rehospitalized. Colonoscopy and biopies were performed and revealed universal ulcerative colitis without malignant changes. Liver biopsy showed chronic active hepatitis. Latex fixation and VDRL became negative. The patient was discharged on prednisone 20 mg. daily. Eight months after initiating prednisone therapy the patient had no major systemic complaints and her complete blood count, coagulation profile, protein and immunoelectrophoresis and liver chemistries are all within normal limits (Figs. 1 and 2). There is no longer any evidence of the purpuric lesions.

COMMENT

This communication describes a patient whose chronic active hepatitis and ulcerative colitis were complicated by several unusual features. Eosinophilia has been previously described with CAH[4] and UC.[5] Review of the literature on eosinophilia and CAH or UC, however, failed to reveal any patient with the level of eosinophilia observed in this patient. Marked eosinophilia (greater than 1,500 cells/cu. mm.) has most frequently been associated with allergic reactions (including drugs) and parasitic diseases and less commonly with bacterial and viral infections, blood dyscrasias, carcinoma and collagen vascular diseases,[6] presumably as part of the over all immunological response to these conditions. In addition, a group of systemic diseases of unknown etiology collectively called the "hypereosinophilic syndromes" is recognized in the differential diagnosis of the blood picture.[6] None of the above diseases was demonstrable in this patient and we conclude that the hypereosinophilia was indeed a secondary feature of the CAH or UC.

Purpuric lesions have been previously described in association with CAH and biopsies of these lesions may reveal vasculitis.[2] Necrotizing vasculitis has also been seen in UC.[5] The lesions in our patient began as urticarial lesions on the lower extremities which later became purpuric. They resembled both grossly and microscopically those previously seen with CAH. Biopsy distinguished them from steroid induced purpura and they did not resemble the lesions reported by Wasserman.[5] In addition, they were indistinguishable from the lesions reported by Klye, et al[7] in their discussion of benign hypergammaglobulinemic purpura or Waldenstrom. They divided their cases into primary (idiopathic) and secondary forms (associated with other diseases, often autoimmune). Interestingly, all of their patients had positive tests for rheumatoid factor of an Ig-G type. Latex fixation was also positive in our patient but the type of immunoglobulin was not determined. Other causes of nonthrombocytopenic purpura, such as cryoglobulinemia, were excluded in our patient.

This patient had several serologic abnormalities usually associated with autoimmune diseases (positive rheumatoid factor, biological false positive VDRL) which all resolved with steroid administration. Since the patient had no antinuclear antibodies and a negative *lupus* preparation, the diagnosis of systemic *lupus erythematosus* was excluded.

The pathogenesis of the concurrence of UC and CAH remains speculative, as does the etiology of their associated epiphenomena but recent interest has centered on the possible roles of antigen-antibody complexes and abnormally reactive T-lymphocytes in these diseases.[3, 8]

We have presented a patient with CAH and UC and the unusual combination of hypereosinophilia, serologic abnormalities and hypergammaglobulinemic purpura, all of which responded dramatically to high dose oral corticosteroid administration. While each of these individual conditions has been previously reported with CAH and UC, their simultaneous appearance in this patient lends support to the thesis that they indeed represent expressions of an abnormal host immunological response to as yet unknown stimuli.

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Clinical Vignette

Cancer of the Colon as a Late Sequel of Pelvic Irradiation

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A patient, who developed carcinoma of the rectum nine years following therapeutic radiation for pelvic malignancy is presented. The relationship of radiation to carcinoma of the colon is reviewed. This relationship makes rigorous follow-up of patients with radiation induced chronic proctocolitis essential.

INTRODUCTION

Radiation therapy has been reported to be a predisposing factor in the development of carcinoma. Cancers of the skin, thyroid, breast, salivary gland, bone marrow, lung, uterus, cervix, bladder and colon have all been reported to follow radiotherapy.[1] In addition, radiation can have effects on the colon which may mimic carcinoma clinically and radiographically.[2] Frequent screening may therefore be necessary to diagnose early malignancy.

CASE REPORT

In 1958 a 36-year old white woman was treated for carcinoma of the cervix with total hysterectomy. In 1966 the patient had a recurrence of the tumor in the vaginal cuff and was treated with an undetermined amount of radiotherapy. Subsequent to that time the patient had episodes of diarrhea intermittently accompanied by blood, mucous and tenesmus. Barium enema (Figs. 1 and 2) and sigmoidoscopic findings were compatible with radiation proctitis, colitis and enteritis. The patient was symptomatically controlled on Lomotil,® steroid enemas and intermittent prednisone.

In April, 1975 the patient had a further episode of rectal bleeding. Sigmoidoscopy at this time revealed a 4 mm. sessile polyp at 13 cm. which was biopsied and disclosed carcinoma. (Figs. 3, 4 and 5). The area was fulgurated locally with electrocautery. In the ensuing 18 months the patient has been followed with four sigmoidoscopies with biopsy, with persistent radiation changes but without evidence of recurrent carcinoma.

COMMENT

Injury to the colon and rectum not uncommonly follows therapeutic irradiation. In the acute stage there is edema and inflammation of the rectal mucosa, sometimes with associated friability. Histologically, changes occur in the crypt epithelium which may have marked cellular atypia and can be confused with superficial carcinoma. These acute changes may progress to frank ulceration but usually resolve spontaneous-

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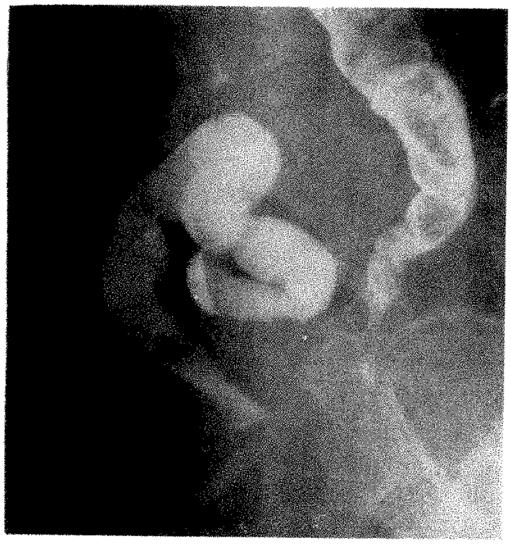

Fig. 1—Barium enema revealing narrowing with lack of distensibility of rectosigmoid and with increase in presacral space—changes compatible with chronic radiation bowel diseases.

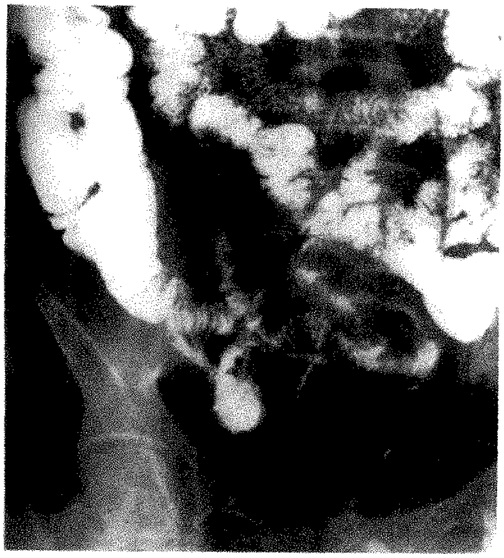

Fig. 2—Small bowel series with spiculization and compatible with radiation enteritis.

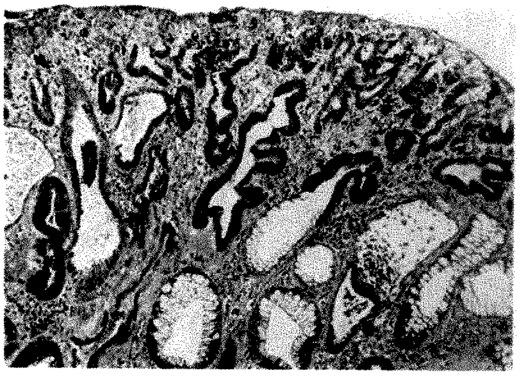

Fig. 3—Atrophic glands composed of goblet cells are seen at the right. Atypical, budding, hyperchromatic glands are seen to replace the normal glands elsewhere (Hematoxylin and eosin, original magnification x84).

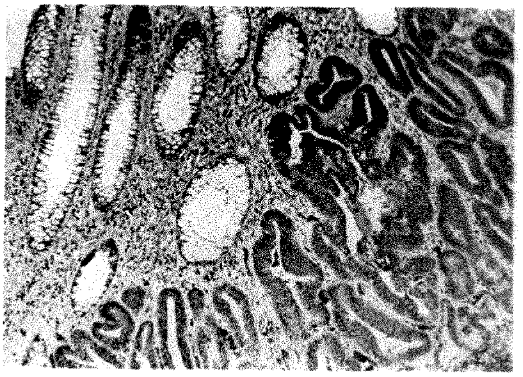

Fig. 4—Proliferation of atypical glands at right are destroying lamina propria and crowding out normal glands (Hematoxylin and eosin, original magnification x4).

ly. Healing takes place with granulation, telangiectasias and eventual stenosis. Pathologically this appears to be due to an obliterative endarteritis with hyalinization of the connective tissue. These late changes have been reported from two months to 30 years after irradiation. The patients may have chronic proctocolitis with diarrhea, mucus, blood and tenesmus or symptoms of pain and constipation secondary to stenosis and stricturing. Fistulization to the bladder or vagina can also occur.[2, 3]

In 1957 Southwick and Slaughter described two cases of adenocarcinoma of the colon following irradiation.[4] Smith in 1962, added three additional cases and Black and Ackerman reported another patient with this late complication of successful radiotherapy occurring 18 years after radiation for carcinoma of the cervix.[5, 6] Castro, Rosen and Quan reviewed their experience

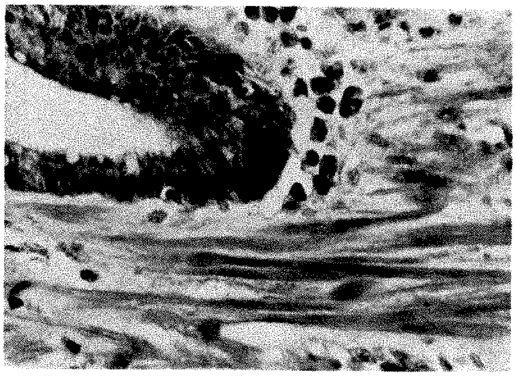

Fig. 5–Neoplastic gland invading horizontal fascicles of muscularis mucosae (lower third of picture) (Hematoxylin and eosin, original magnification x340).

with 26 patients who developed carcinoma of the colon and rectum following irradiation for cervical and uterine carcinoma.[7] They found that in all cases at least five years elapsed between radiation and the development of carcinoma. This correlates well with the delayed onset of carcinoma after irradiation of other tissues. In only one case did carcinoma develop in the absence of clinical or histologic evidence of radiation proctitis. In this small series the five-year survival after the diagnosis of colorectal carcinoma was only 20%. Our patient parallels this experience. Her carcinoma developed after a nine-year period of clinically, radiographically and histologically evident radiation induced proctocolitis.

With more patients surviving pelvic irradiation for long periods, the problem of postradiation carcinoma may become a more significant problem for the physician managing the patient with radiation induced proctocolitis. Patients in this group should be watched carefully and evaluated fully for changes in bowel habits. Routine surveillance for the development of malignancy is indicated although the best "formula" for sigmoidoscopy, biopsy, stool for occult blood, barium enema or colonoscopy has yet to be determined.

SUMMARY

While there is no definitive proof that carcinoma of the colon is a result of pelvic radiation, the well documented association of radiation with other types of neoplasia and the increasing number of cases in the literature of radiation proctocolitis followed by carcinoma imply that there is a causal relationship. If this is indeed the case, particular vigilance on the part of the physician is called for in five-year survivors of pelvic irradiation since the symptoms of radiation induced proctocolitis may mimic those of carcinoma of the colon and rectum.

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Clinical Vignette

Mucinous Carcinoid and Endometriosis in an Inside-out Appendix

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This is the first report of the simultaneous occurrence of mucinous carcinoid and endometriosis in an inside-out appendix. The literature concerning carcinoids, endometriosis and intussusception of the appendix is reviewed. The mucinous, or goblet cell carcinoid was positive for mucin, argentaffin and argyrophil stains. Paneth cells were present. Two and one-half years with no tumor recurrence suggest good prognosis as previously reported.

INTRODUCTION

A mucinous carcinoid[1] and goblet cell carcinoids[2] of the vermiform appendix have been reported. Review of the literature reveals a case of endometriosis of the appendix and asymptomatic carcinoid,[3] four cases of complete inversion of the appendix and endometriosis,[4] one case of complete inversion of the appendix and carcinoid[5] and one case of intussusception of the appendix and carcinoid.[6] This is the first report of the simultaneous occurrence of mucinous carcinoid and endometriosis in an inside-out appendix.

CASE REPORT

A 41-year old white female complained of intermittent right lower quadrant pain six months and four weeks prior to admission. There was no history of right lower quadrant pain associated with menses. Barium enema and air contrast studies revealed a filling defect in the cecum. Laboratory data was non contributory except for a WBC count of 11,000/cu. mm. Chest x-ray showed a calcified nodule consistent with granulomatous disease from coccidioidomycosis 16 years previously. Physical examination revealed tenderness and a palpable mass in the right lower quadrant. Exploratory laparotomy revealed that the cecum contained a hard polypoid lesion about the size of an olive. No appendix could be seen on the outside of the cecum. Careful inspection revealed a small opening with fat corresponding with the mesentery of the appendix which was completely inverted. The intussusception could not be reduced and colotomy followed. A total abdominal hysterectomy was performed for large uterine leiomyomata. The patient improved gradually and has done well since the operation two and one-half years ago with no tumor recurrence

PATHOLOGIC FINDINGS

Gross characteristics:—A 5 x 2 cm. tan markedly edematous inside-out appendix with a lumen lined by serosa and

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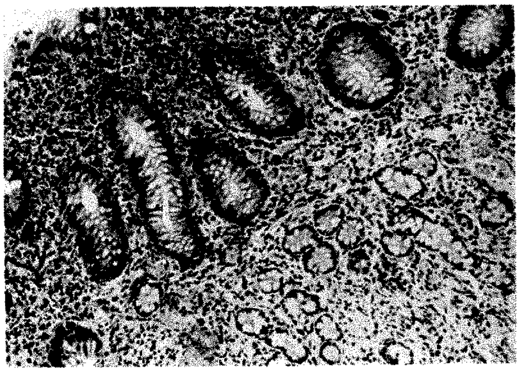

Fig. 1—Mucinous carcinoid tumor nests and glands infiltrating the wall of the appendix (hematoxylin and eosin, original magnification x125).

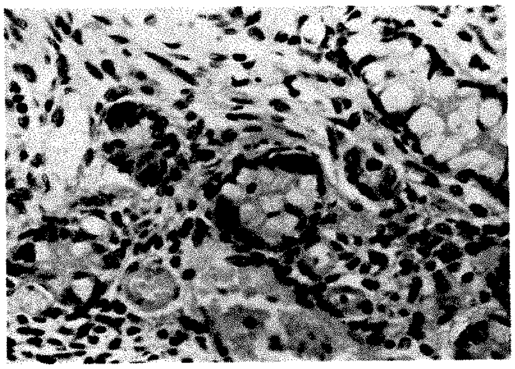

Fig. 2—Neoplastic acini containing Paneth cells (hematoxylin and eosin, original magnification x400).

a purple-gray thickened distal portion. No tumor was identified grossly.

Microscopic features:—The appendix revealed two distinct lesions: mucinous carcinoid and endometriosis. A well differentiated epithelial neoplasm composed of solid nests and glands infiltrated all layers of the wall (Fig. 1). At first the appearance of the tumor was confused histologically with heterotopic gastric glands. The tumor nests were rounded or elongated, composed of cells with either vacuolated, or slightly granular cytoplasms. Paneth cells were found frequently in the neoplastic acini (Fig. 2). Mitoses were absent. The nuclei were small, round, occasionally showed tiny nucleoli and were located toward the periphery of tumor cells. Tumor cells were present in lymphatics and periappendiceal fat. There were islands of endometrial tissue with glands and surrounding stroma present throughout the thickened muscular wall along with the infiltrating tumor cell nests (Fig. 3). The tumor cells were mucin positive, Alcian blue positive and periodic acid-Schiff positive with or without diastase digestion. Some tumor cells were positive for argentaffin and argyrophil stains. Argentaffin positive cells were mostly correlated to the more granular, or nonvacuolated cells (Fig. 4). No electron microscopic studies were performed, because the presence of tumor was an unexpected histologic finding.

COMMENT

The patient presented with intermittent right lower quadrant pain not associated with menses. Barium enema revealed a filling defect in the cecum, and an inside-out appendix was found at operation. Hill et al[4] reported two cases of type 5 intussusception, inside-out, or complete inversion of the appendix associated with endometriosis. Their review revealed two more cases of endometriosis in 13 inside-out appendices. Uohara and Kovara[7] reported 12 cases of endometriosis of the appendix as a result of incidental appendectomy without symptoms and five cases with symptoms suggestive of chronic or cyclic appendicitis. Panganiban and Cornog[3] reported that endometriosis and associated muscular hyperplasia of the appendix act as a foreign body mass and appendiceal peristalses caused complete inversion and intussusception of the appendix into the cecum. They concluded that intussusception is a rare but important complication of endometriosis, usually asymptomatic and an incidental finding in

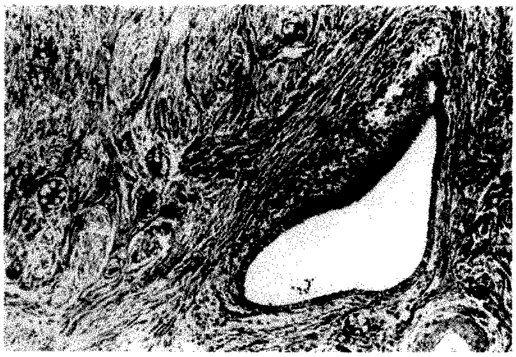

Fig. 3—Endometrial gland and infiltrating mucinous carcinoid tumor cells (Hematoxylin and eosin, original magnification x125).

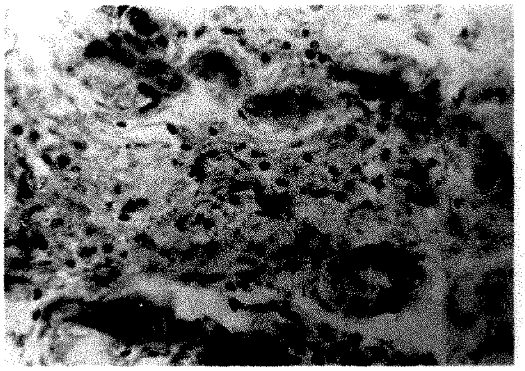

Fig. 4—Argentaffin and Alcian blue mucin positive tumor cells (Fontana-Masson, Alcian blue, original magnification x400).

patients with pelvic endometriosis. They found a high incidence of endometriosis associated with uterine leiomyoma. The patient reported here had intermittent right lower quadrant pain on two occasions five months apart, uterine leiomyomata and inside-out, totally intussuscepted appendix with endometriosis, and a mucinous carcinoid infiltrating the wall. Pelvic endometriosis was not present.

The main reason for operation in this case was the filling defect of the cecum and suspicion of carcinoma. Howard, et al[8] reported two cases of intussusception of the appendix in which the inverted appendix formed a polypoid filling defect simulating carcinoma of the cecum. Schmidt and McCarthy[9] reported a case of asymptomatic compound intussusception of the appendix associated with endometriosis in a patient with right lower quadrant pain, and two normal roentgenographic studies of the colon.

Carcinoid tumors of the appendix associated with intussusception have been reported by Hickinbotham[5] and Purita.[6] These tumors were not associated with endometriosis and were not mucinous carcinoids. Panganiban and Cornog[3] reported an incidental asymptomatic carcinoid tumor with endometriosis of the appendix without intussusception. There are no reported cases of simultaneously occurring carcinoid tumor, endometriosis and intussusception of the appendix. Specifically there are no reported cases of mucinous carcinoid tumors and endometriosis and/or intussusception of the appendix, or all three pathological conditions combined.

A mucinous carcinoid tumor of the appendix was reported by Klein.[1] The microscopic findings of tumor were unexpected and similar to those reported in this case. Paneth cells were not described. A related and very similar tumor of the appendix, composed of well differentiated mucin-secreting glands with no argentaffin or argyrophil granules, was reported by Rosai and Rodriguez.[10] Dense round granules typical of Kulchitsky cells were evident on electron microcopy studies and the lesion was classified as carcinoid. Droga, et al[11] reported a case of heterotopic gastric and esophageal tissue in the appendix. The glands described in that report could be easily confused histologically with mucinous carcinoid except that polypoid lesions with typical gastric tissue, fundic-type glands, Paneth cells and parietal cells were evident. Nonkeratinizing stratified squamous epithelium lined the distal appendix overlying deep clusters of mucous glands considered evidence of esophageal tissue. Subbuswamy, et al[2] reported 12 tumors of the appendix as goblet cell carcinoids, because the main cell type resembled the normal goblet cell of the intestinal tract. The tumors showed intramural position in the appendix, argentaffin cells, copious mucin production and cells with eosinophilic granules regarded as Paneth cells. Paneth cells were also strikingly present in the tumor glands throughout the wall of the appendix in our case. The tumors were thought to be comparable to argentaffin and and nonargentaffin tumors of the appendix.[12] Abt and Carter[13] reported a goblet cell carcinoid of the appendix and demonstrated mucin and enterochromaffin granules within the same cells, as previously demonstrated by Hernandez and Fernandez[14] in a mucus-secreting colonic carcinoid. They believe that goblet cell carcinoids of the appendix should be treated by simple appendectomy, since their behavior is similar to appendiceal carcinoids. The mucinous carcinoid reported here was positive for mucin, argentaffin and argyrophil stains. The patient had a colotomy without tumor recurrence after two and one-half years and prognosis is considered good. The patient had uterine leiomyomata and no other tumors, even though patients with carcinoid are known to have other associated carcinoids, or second primary cancers.[15, 16] Ackerman and Rosai[17] refer to mucinous and goblet cell carcinoid tumors of the appendix with no distinction and point out that they are associated with the same indolent clinical course and good prognosis as ordinary carcinoids of the appendix.

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The Pediatric Corner

THE VARIED MANIFESTATIONS OF CROHN'S DISEASE IN CHILDREN AND ADOLESCENTS

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Thirty children less than 15 years of age with Crohn's disease are reported. The mean age of onset was nine years and five months. Delay in diagnosis may stem from the varying modes of presentation. The mean delay in diagnosis was two years. Chronic diarrhea and/or recurrent abdominal pain associated with extraintestinal manifestations, particularly abnormalities of growth and development suggests the possibility of Crohn's disease in the pediatric age group. Involvement of the terminal ileum occurred in 29 of the 30 patients. In addition, colonic disease occurred in 13 and jejunal involvement in one. Four patients presented with an acute onset of their disease. A favorable response to either medical or surgical therapy occurred in all four. Twenty-six patients had an insidious onset and tended to have a chronic course despite either medical and/or surgical therapy. Thirteen patients had an intestinal resection, with recurrence occurring in three from 1-4 years postoperatively. To date there has been one death.

INTRODUCTION

Despite references in the adult literature to the onset of Crohn's disease in childhood, the pediatric literature has only sporadically reviewed the manifestations of Crohn's disease in children.[1-3]

The purpose of this review is to report our experience with 30 children with regional enteritis seen over a ten-year period and to focus on the various modes of presentation of this disease in children. In addition, certain differences between the pediatric and adult patient with Crohn's disease will be stressed.

PATIENT MATERIAL

Thirty consecutive cases of Crohn's disease in children less than 15 years of age

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Supported in part by a grant (RR-69) from the General Clinical Research Center, Program of the Division of Research Resources, National Institutes of Health.

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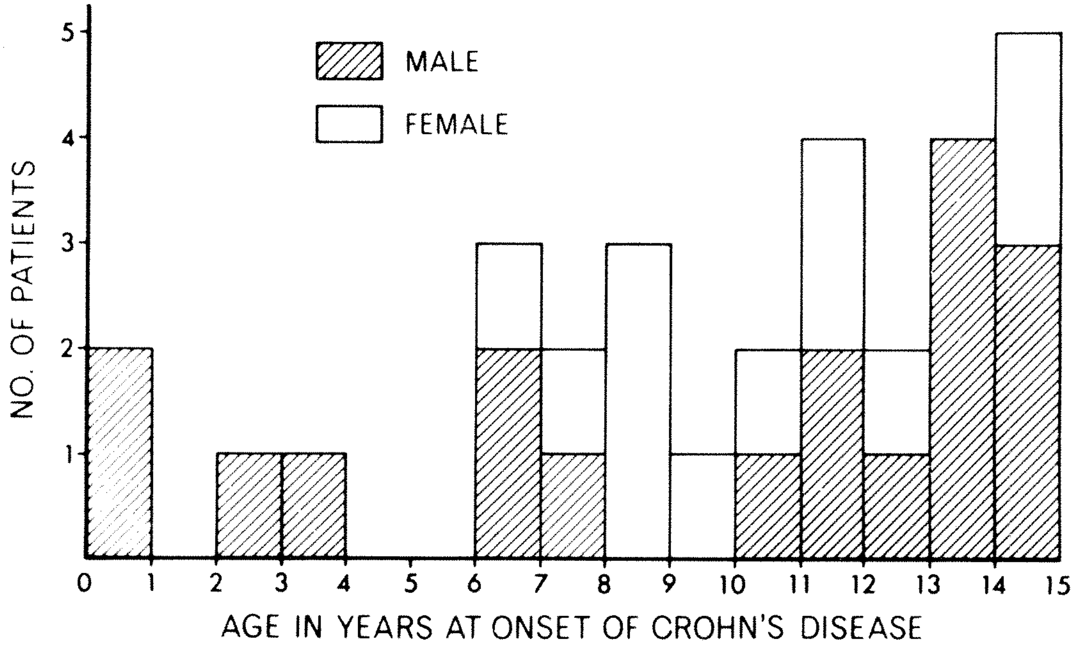

Fig. 1—Sex incidence and age in years at onset of 30 children with Crohn's disease.

presenting at the University of Colorado Medical Center and Denver Children's Hospital between 1964 and 1973 were reviewed. The criteria for establishing the diagnosis was either by gross pathological findings at surgery, with or without histologic confirmation, or by radiological studies demonstrating typical changes of Crohn's disease.[4]

The group was composed primarily of referral patients from a large geographic area. The age of the patients at the onset of the disease and the sex distribution are represented in Figure 1. The mean age of onset was nine years and five months. There were 18 males and 12 females. The delay in diagnosis is shown in Figure 2. The mean delay was two years.

Four patients presented acutely with no previous gastrointestinal symptomatology. Two of these patients were thought to have acute appendicitis. One other presented with acute intestinal obstruction and another with manifestations secondary to protein-losing enteropathy.

The remaining 26 patients had an insidious onset of their disease with gastrointestinal symptoms of varying degree. Four of these 26 patients were diagnosed at laparotomy for suspected acute appendicitis superimposed upon chronic gastrointestinal complaints. The remaining 22 patients had a spectrum of gastrointestinal complaints, such as diarrhea, abdominal pain, anorexia, abdominal mass or perianal disease. In seven of these patients, however, the complaints were so overshadowed by extraintestinal manifestations that they were not felt to be of significance.

Gastrointestinal manifestations occurring at some time in the course of our 30 patients are illustrated in Figure 3. In addition, 13 patients were examined proctoscopically for suspected rectal involvement. Seven were found to have increased friability and in three this was more marked proximally.

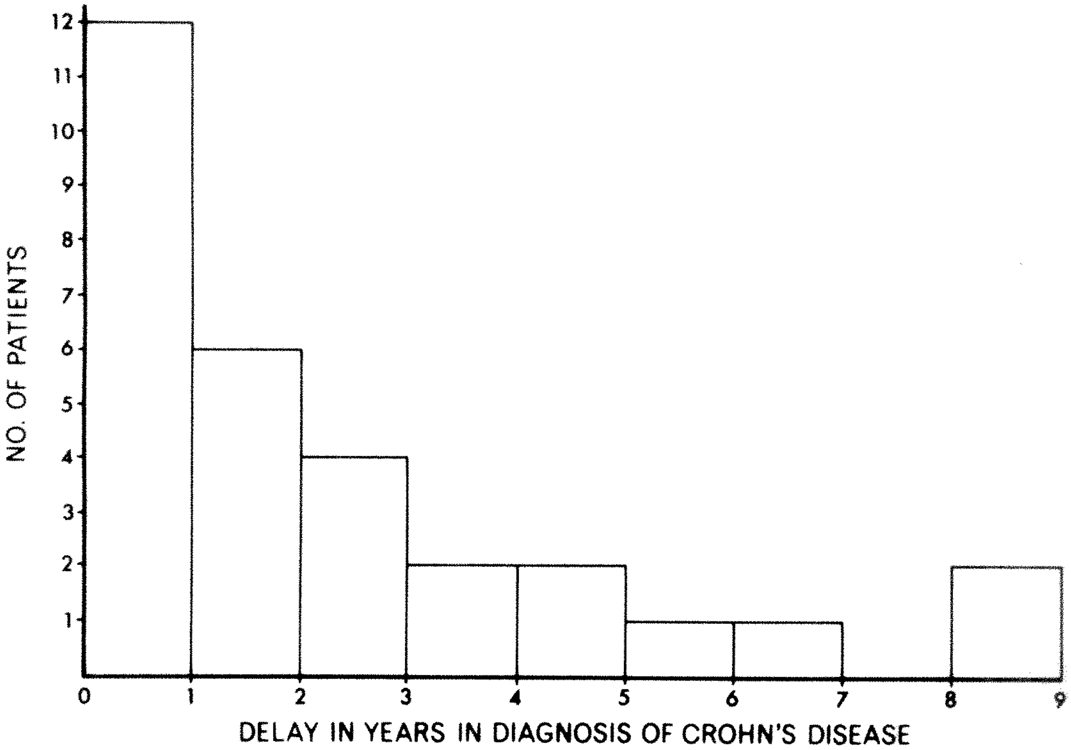

Fig. 2—Delay in years in the diagnosis of Crohn's disease.

The various extraintestinal manifestations were shown in Figure 4. In addition, digital clubbing was present in 25% of the patients.

LABORATORY AND RADIOGRAPHIC STUDIES

At the time of diagnosis, the hematocrit ranged from 27-48 with a mean of 36. Platelet counts were recorded in 12 patients and thrombocytosis (platelet count greater than 500,000 cu./mm.) was noted in eight. Platelet counts ranged from 204,000-3,850,000 cu./mm. The sedimentation rate was elevated in 22 of 27 patients and ranged from 6-110 mm./hr. with a mean of 42.

Terminal ileal involvement was documented radiographically and/or surgically in 29 of 30 patients. An upper gastrointestinal series and small bowel follow-up, rather than the barium enema, appeared to be the most rewarding in documenting disease of the terminal ileum. Colonic involvement was demonstrated in 13 of 30 patients by either barium enema and/or proctosigmoidoscopy. One patient had upper jejunal involvement in addition to ileal and colonic disease.

TREATMENT AND COURSE

Medical therapy was instituted in 23 of 30 patients for varying criteria. In 15 a combination of Azulfidine® and prednisone was employed. Two received Azulfidine and six prednisone alone. Corticosteroids were not employed primarily in the former two patients because of a concern for untoward side-effects. In general, prednisone was used alone in small dosage in those patients with predominate extraintestinal manifestations. In addition five patients re-

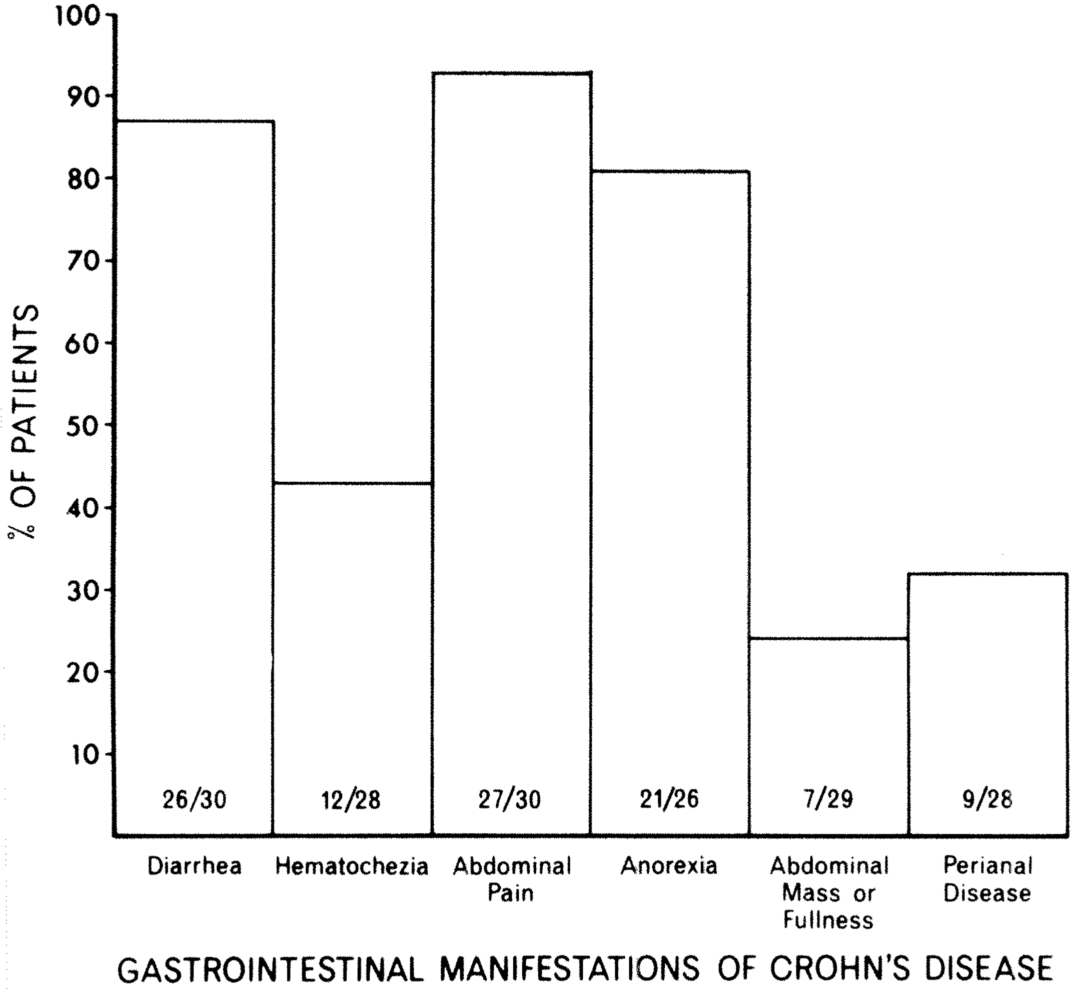

Fig. 3—Incidence of gastrointestinal manifestations in 30 children with Crohn's disease.

ceived azathioprine, when other medical therapy was of no apparent benefit.

Seventeen of 30 patients underwent exploratory laparotomy for a variety of indications, such as suspected acute appendicitis, or complications of their disease. The latter included, intestinal obstruction, fistula formation, failed medical therapy and/or significant disturbance of normal growth and development.

Thirteen patients had an intestinal resection. Two of these had an acute onset of their disease with suspected acute appendicitis. The remaining 11 had complicated chronic disease and three of these required further resection, because of distal recurrence of their disease from 1-4 years postoperatively. Five of the 13 who underwent intestinal resection were lost to follow-up within 12 months of their operation, while still asymptomatic.

Six of the 30 patients had appendectomies. Two had an acute onset of their disease. The remainder had an insidious onset and one of these developed a fistula postoperatively. Four of the six patients who had an appendectomy had an intestinal resection. In two patients laparotomy

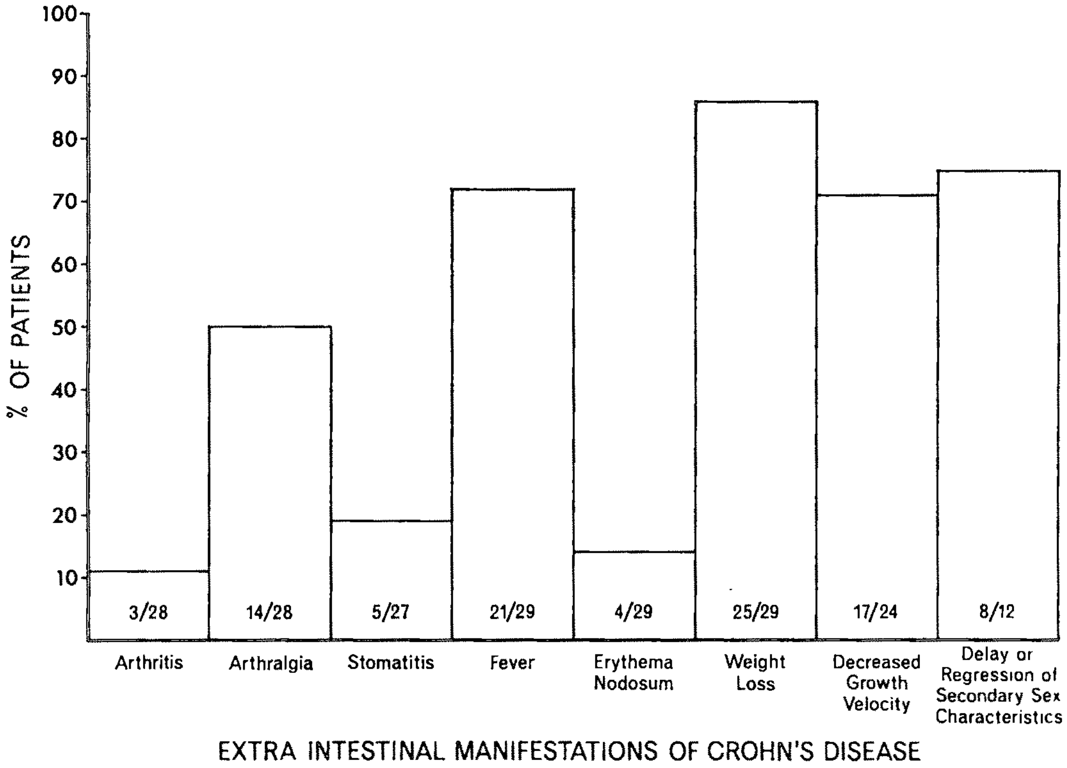

Fig. 4—Incidence of extraintestinal manifestations in 30 children with Crohn's disease.

was performed but resection was deemed impossible because of extensive disease.

Of the four patients with an acute onset, three were lost to follow-up within 12 months, at which time all were asymptomatic, the fourth patient remitted following the institution of azathioprine, in addition to Azulfidine and corticosteroids, and has remained well over a three-year period of follow-up.

The 26 patients with an insidious onset ran a course which tended to be relapsing and remitting in nature and independent of medical therapy, however, follow-up was often inadequate.

To date there has been only one death (Case 4).

CASE REPORTS

Case 1:—N. D. is a white female who presented at 15 years of age with acute right lower quadrant pain and fever. During the preceding six months she had complained of intermittent diarrhea without blood and had noted postprandial crampy abdominal pain. Preoperative diagnosis was acute appendicitis but at surgery she was found to have an inflamed portion of terminal ileum, cecum and ascending colon. An area of about 8 cm. was resected and the patient did well in the immediate postoperative period. Histological examination revealed regional enteritis. Several weeks after surgery, however, she developed bloody diarrhea with exacerbation of her abdominal pain and progressive weight loss. A barium enema revealed total colonic disease.

Despite various combinations of Azulfidine, prednisone, Lomotil® and Imuran® therapy the patient had continuous bloody diarrhea over the ensuing five years. In addition to her gastrointestinal complaints and delayed growth pattern, she developed extreme photophobia, amenorrhea and easy bruisability with development of ecchymoses. Barium enema examination at age 20 revealed severe total colonic involvement with a normal ileum proximal to the area of previous anastomosis.

Comment:—Acute abdominal pain, which is superimposed upon chronic intestinal or extraintestinal complaints, especially abnormalities of growth and development,[5, 6] should alert the pediatrician to the possibility of Crohn's disease. Surgical resection in patients with ileal involvement and chronic disease in contrast with the acute form of regional enteritis not uncommonly leads to recurrence and/or extension of the disease.[1, 4, 7]

Case 2:—J. T. is a white male who presented at age 14 with an eight-year history of "juvenile rheumatoid arthritis". At the onset of his illness the patient developed malaise, fever, anorexia and painful, inflamed and swollen ankles and knees. He also had a 9 kg. weight loss. During the ensuing six years he suffered approximately two severe exacerbations of joint inflammation each year. These were treated with salicylate therapy. There was a marked deceleration in growth velocity and his weight fell from the 97% to far below the 3%. Appetite was reported as normal but the stools were noted to be particularly foul smelling since the age of 12 years. Examination revealed a thin child with digital clubbing, mild scoliosis and bilateral joint deformities of the ankles and knees. Hematocrit was 28, sedimentation rate 50 mm./hr. and upper gastrointestinal and small bowel series demonstrated changes consistent with regional enteritis.

During a three-year follow-up period, the patient has been maintained on Azulfidine with little gastrointestinal symtomatology. Infrequent joint exacerbations have been well controlled with intermittent prednisone therapy. The patient's growth rate continued to be slow and he remains prepubertal.

Case 3:—L. H. is a white male who presented at 11 years of age with the chief complaint of a two-month history of progressive, severe stomatitis. In addition, the patient had noted intermittent diarrhea and abdominal cramps for about six months. Concurrent with the onset of the stomatitis was the development of *erythema nodosum* and conjunctivitis. On examination he appeared chronically ill and mild digital clubbing, right lower quadrant guarding, and anal fissures were noted. An upper gastrointestinal and small bowel series confirmed the diagnosis of regional enteritis. Platelet count was 531,000/cu. mm.; sedimentation rate 50 mm./hr. and hematocrit 35.

He was started on Azulfidine and tetracyclinehydrocortisone gargles and within two weeks a marked improvement in the diarrhea and abdominal cramps were noted. The oral and conjunctival lesions had cleared. During a two-year follow-up period, the patient remained symptom free on Azulfidine and demonstrated normal growth velocity and weight gain.

Comment:—Extraintestinal manifestations such as fever,[3] arthritis;[8] arthralgia, digital clubbing;[9] stomatitis, conjunctivitis and *erythema nodosum* are more common in children than adults with Crohn's disease. They appear to be independent of the severity of the bowel disease and often may precede the gastrointestinal symptoms. Extraintestinal manifestations usually respond to corticosteroid therapy.

Case 4:—S. F. was a white female who presented at 11 years of age with a one-year history of a 9 kg. weight loss, frequent vomiting and anorexia. A diagnosis of *anorexia nervosa* was considered and the patient received psychotherapy. After one year she developed postprandial abdominal pain and 3-4 loose stools per day. Laboratory investigation at this time revealed a sedimentation rate of 26; serum carotene of 36 μgm.%; a serum albumin of 2.8 gm./100 ml. and a small bowel series revealed abnormalities in the terminal ileum consistent with regional enteritis.

During the ensuing five years the patient did poorly despite Azulfidine and prednisone therapy. She failed to gain weight, did not develop secondary sex characteristics and had primary amenorrhea. Repeat small bowel series on several occasions revealed continuous proximal extension of her disease. Barium enemas consistently showed no colonic involvement.

Exploratory laparotomy was undertaken at 17 years of age, but no resection was possible because of extensive small bowel disease. Only 60 cm. of small bowel was felt to be uninvolved. Following surgery the patient was placed on Imuran and parenteral hyperalimentation, however, she had a rapidly downhill course with pelvic abscesses, a cerebral vascular accident, sepsis, pneumonia, and death approximately one and a half months following surgery.

Comment:—Anorexia is a common manifestation of Crohn's disease[10] and directly relates to the occurrence of postprandial, crampy abdominal pain and fullness. Low grade fever, a common extraintestinal manifestation of Crohn's disease in children and anemia are contributory factors.

An elevated serum carotene may be of value in differentiating *anorexia nervosa* from Crohn's disease.[11]

Although recurrence and/or extension of the disease process is not uncommon following intestinal resection, radiological extension prior to surgery only occurs rarely.[4]

Case 5:—P. G. is a white female who presented at 11 years of age with a one-month history of sore throat, frequent headaches, occasional "gas pain", and increasing fatigability and was at that time found to have a hematocrit of 27; a platelet count a 3,850,000/cu. mm. and a sedimentation rate of 52 mm./hr. Collagen vascular studies were negative and bone marrow examination revealed "very severe megakaryocytic hyperplasia". Chest x-ray revealed a diffuse interstitial infiltrate which persisted radiographically for about four months. Over the next six months, in addition to her initial symptoms, she complained of arthralgia and occasional diarrhea. Her anemia, thrombocytosis (platelet counts greater than 1,000,000) and elevated sedimentation rate persisted and, eight months after her initial presentation, an upper gastrointestinal and small bowel series was obtained and revealed findings of regional enteritis. During this eight-month time interval, there had been no change in the patient's height or weight.

Following initiation of Azulfidine therapy the patient noted a marked improvement in her energy and a disappearance of her mild gastrointestinal complaints, however, hematological studies were unchanged. With the addition of prednisone her laboratory data obtained three months after the diagnosis of regional enteritis was established, revealed a hematocrit of 40.4; platelet count of 220,000 and a sedimentation rate of 7 mm./hr.

Comment:—Thrombocytosis is a common but infrequently reported manifestation of chronic inflammatory bowel disease and appears to correlate with the activity of the bowel disease.[12, 13]

DISCUSSION

Although not specific, chronic diarrhea and recurrent abdominal pain are common manifestations of Crohn's disease in both adults and children and in the present series were present in from 80-90% of the patients. It has been stressed, however, that in children extraintestinal manifestations may predominate initially and lead to significant delay in diagnosis.[3, 4] Indeed, this was the case in seven of the children reported here.

Increased awareness of the disease decreases the delay in diagnosis,[3] however, radiological confirmation may be difficult even in symptomatic patients. In one patient in our series, radiological confirmation required over five years despite significant gastrointestinal symptoms.

The concurrence of chronic diarrhea and/or recurrent abdominal pain with deceleration of growth velocity and delay in development or regression of secondary sex characteristics should alert the pediatrician to the possibility of Crohn's disease, particularly in the presence of other extraintestinal manifestations such as arthritis, stomatitis and prolonged fever, or laboratory evidence of chronic inflammation (i.e. elevated sedimentation rate, absolute platelet count or serum gamma globulin).

Abnormalities of growth and development occurred in from 70-80% of the patients in the present series and account for the major difference between children and adults with Crohn's disease. Furthermore, other extraintestinal manifestations, particularly chronic low grade fever, are more common in children than adults.[3]

The management of Crohn's disease in both children and adults is complex and, in general, should always be individualized.

The effect of medical therapy on the gastrointestinal manifestations of Crohn's disease is quite controversial. Hopefully, data obtained from the National Cooperative Crohn's Disease Study in Adults will be applicable to patients under 15 years of age. It should be stressed, however, that the effect of the disease and the therapeutic regimens on growth and development will probably remain unanswered.

On the other hand, extraintestinal manifestations apart from those abnormalities of growth and development are commonly relieved by corticosteroid therapy. Furthermore, corticosteroids have a beneficial effect on the associated thrombocytosis of Crohn's disease and, interestingly, the latter appears to correlate with the activity of the bowel disease.[12, 13]

Abnormalities of growth and development, which also correlate with the activity of the bowel disease[6] rather than specific hormonal deficiency.[5, 14] may not always be favorably influenced by intestinal resection.[2] Weight gain and growth can be achieved by increased caloric intake (> 80 cal./kg./day). The benefit of surgery, however, should always be carefully weighed against the risk of recurrence of the disease and subsequent development of the short bowel syndrome.

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The Radiology Corner*

BOERHAAVE'S SYNDROME†

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The classic history for patients with spontaneous rupture of the esophagus (Boerhaave's syndrome is that of a middle aged or elderly man who overindulges in food or drink, vomits and experiences sudden onset of substernal, left chest or epigastric pain followed shortly thereafter by dyspnea, diaphoresis, shock and fever and the development of subcutaneous emphysema. On physical examination, the patient is very sick and a "mediastinal crunch" is heard. This stereotype, however, may be misleading. Other causes in addition to vomiting have been implicated in the production of Boerhaave's syndrome including straining during defecation or weight lifting, grand mal seizures and blunt abdominal trauma.[1, 2] The common denominator in all of these is elevation of intragastric pressure usually but not necessarily superimposed on marked to moderate gastric dilatation.[2]

Two other prerequisites are relaxation of the lower esophageal sphincter and persistent contraction of the proximal sphincter (cricopharyngeus).[2] These may occur because of vomiting and there may be other causes as well. In Abbott's series of 47 cases, 14 patients had pre-existing neurologic abnormalities which may have accounted in part for the failure of the proximal sphincter to open.[3] Furthermore, 10 others were alcoholics, a diagnosis which could explain muscular incoordination of the esophagus. It is also of interest that 11 of the 47 patients were hypertensive prior to the episode, so that if they were to come into the Emergency Room with normal blood pressures, relative hypotension might go unnoticed.

Pain is an almost universal feature of Boerhaave's syndrome and it evokes a broad differential diagnosis including dissecting aneurysm, pulmonary embolus, perforated ulcer and pancreatitis. Even the electrocardiographic abnormalities of myocardial infarction have been produced.[4] Evidence that the patient has experienced a catastrophic event should not be required in order to consider the diagnosis. Fever, dyspnea, diaphoresis and hypotension may be late manifestations and their absence early in the course should not militate against making this diagnosis. While hematemesis may occur, it rarely predominates. A mediastinal crunch is often not heard even in patients with pneumomediastinum and may be caused by other conditions.

Lack of a history of vomiting in no way excludes the diagnosis of Boerhaave's syndrome. In two large series approximately one-quarter of the patients gave no such history.[3, 5] Prompt diagnosis is important because, while isolated self-limited cases

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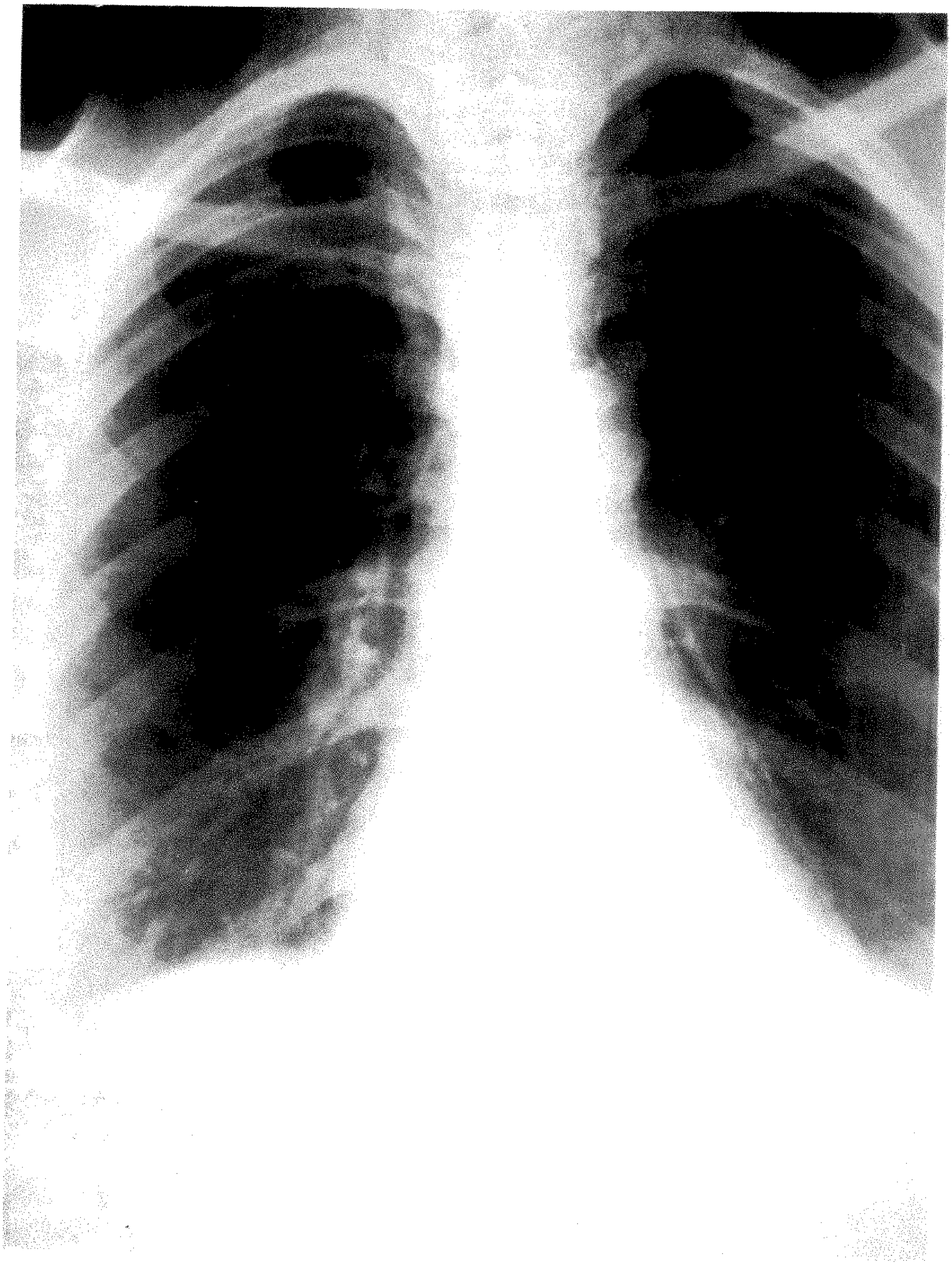

Fig. 1—Chest radiograph in a 38-year old woman with Boerhaave's syndrome showing pneumomediastinum. Note the air along the left heart border. The patient had sudden onset of dyspnea, cough and chest pain initially thought to be due to a pulmonary embolus. The correct diagnosis was made after a gastrografin swallow which revealed extravasation of contrast material from the esophagus.

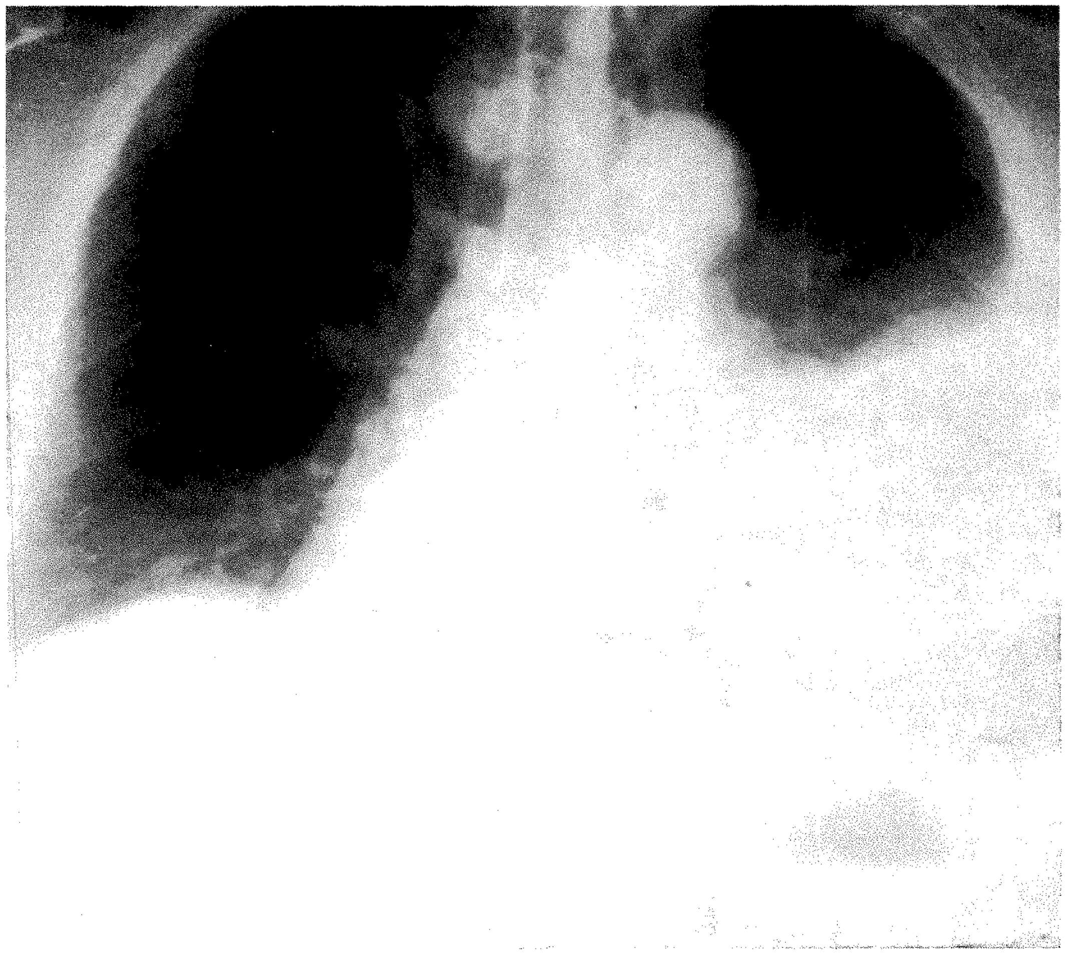

Fig. 2—Chest radiograph in a 62-year old alcoholic showing a massive left pleural effusion and mediastinal and subcutaneous emphysema at the thoracic outlet. The patient had been on an alcoholic binge and had been unconscious. When he awoke he vomited and developed left chest pain.

of Boerhaave's syndrome have been reported,[6] most authorities consider immediate surgery to be essential. The mortality rate rises sharply when treatment is delayed.[3, 5, 7-10] There is less agreement concerning management of iatrogenic perforations.[11, 12]

An understanding of the pathophysiology of Boerhaave's syndrome is important. Most of the tears are longitudinal and occur in the left posterior aspect of the esophagus within a few centimeters of the diaphragmatic hiatus.[2, 13] Two separate tears in the esophagus were found on one occasion.[14] Tears in isolated esophagi occur in this location as well, suggesting that there is an intrinsic weakness in this area and not merely a lack of supporting structures.[15] The muscular coat ruptures first and then the mucosa protrudes through the rent to a varying degree before bursting, spewing the contents of the esophagus into the mediastinum.[2]

Pneumomediastinum may occur within an hour of perforation and it may be the only abnormality on the radiograph (Fig. 1).

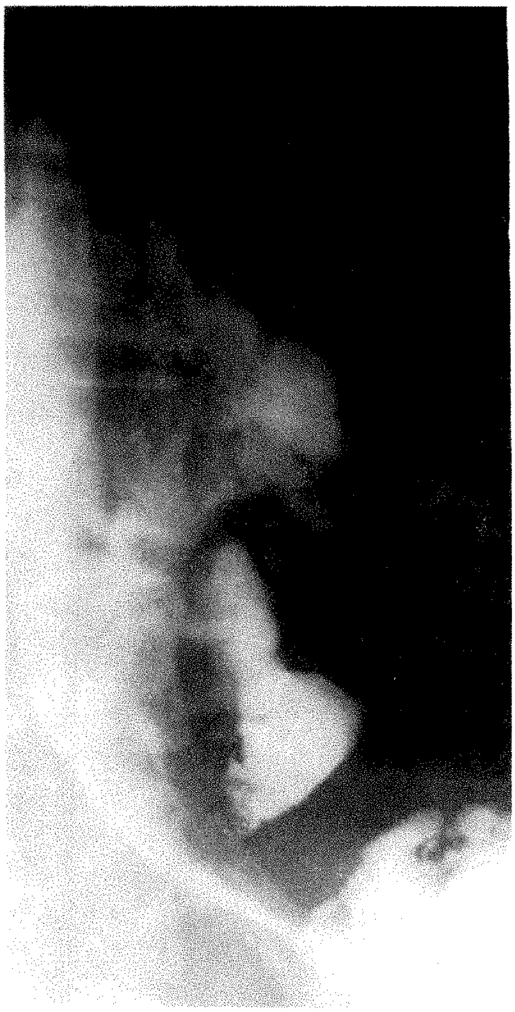

Fig. 3—Esophagram showing extravasation of a large quantity of contrast material into the mediastinum in a patient with Boerhaave's syndrome. The amount of contrast material which leaks from the esophagus varies widely and may even be absent in patients with a rupture of the esophagus.

Parkin states that 9% of patients with Boerhaave's syndrome have a normal chest x-ray throughout their course, so that if warranted by the clinical findings, a contrast examination of the esophagus should be performed despite absence of abnormal radiograph findings.[16]

Air may collect in the lower mediastinum separating the parietal pleura from the hemidiaphragm.[17, 18] As noted by Rogers, et al, predominance of pneumomediastinum along the lower aspect of the aorta and elevating the parietal pleura is suggestive of Boerhaave's syndrome, because air from spontaneous pneumomediastinum is unusual in this location.[2] Visualization of the left hemidiaphragm medially where it is usually obscured by the heart may be another clue to air in the mediastinum or pericardium.[19] Bubbles of air and air-fluid levels in the mediastinum are obviously important because they occur only in Boerhaave's syndrome and not in spontaneous pneumomediastinum where fluid is absent. Often pneumomediastinum is better seen on lateral radiographs of the chest presenting as a thin rim of radiolucency outlining the great vessels.

Subcutaneous emphysema has been estimated to occur in 60% of patients with Boerhaave's disease (Fig. 2).[20] This is one of the diseases that can cause acute widening of the mediastinum.[21] Most patients develop a chemical pleuritis and pneumonitis even when the pleura remains intact.[2, 21] In a patient with chest pain and a retrocardiac infiltrate in the lung, one must remember the possibility of Boerhaave's syndrome and look carefully for pneumomediastinum. Often this is not obvious and radiographs of excellent technical quality and overpenetrated films are essential. Most of the time the pulmonary infiltrate is on the left but the right lung may be involved or the pneumonia may be bilateral. Pleural effusion occurs in 90% of the patients[16, 20] (Fig. 2). In adults, it is usually left-sided originally. In all five infants who were reported with Boerhaave's syndrome, the effusion was on the right.[22] A pleural effusion associated with pneumomediastinum should raise the possibility of the syndrome. When the pH of the pleural fluid is less than 6, it is diagnostic of a ruptured esophagus.[23] Higher pH may

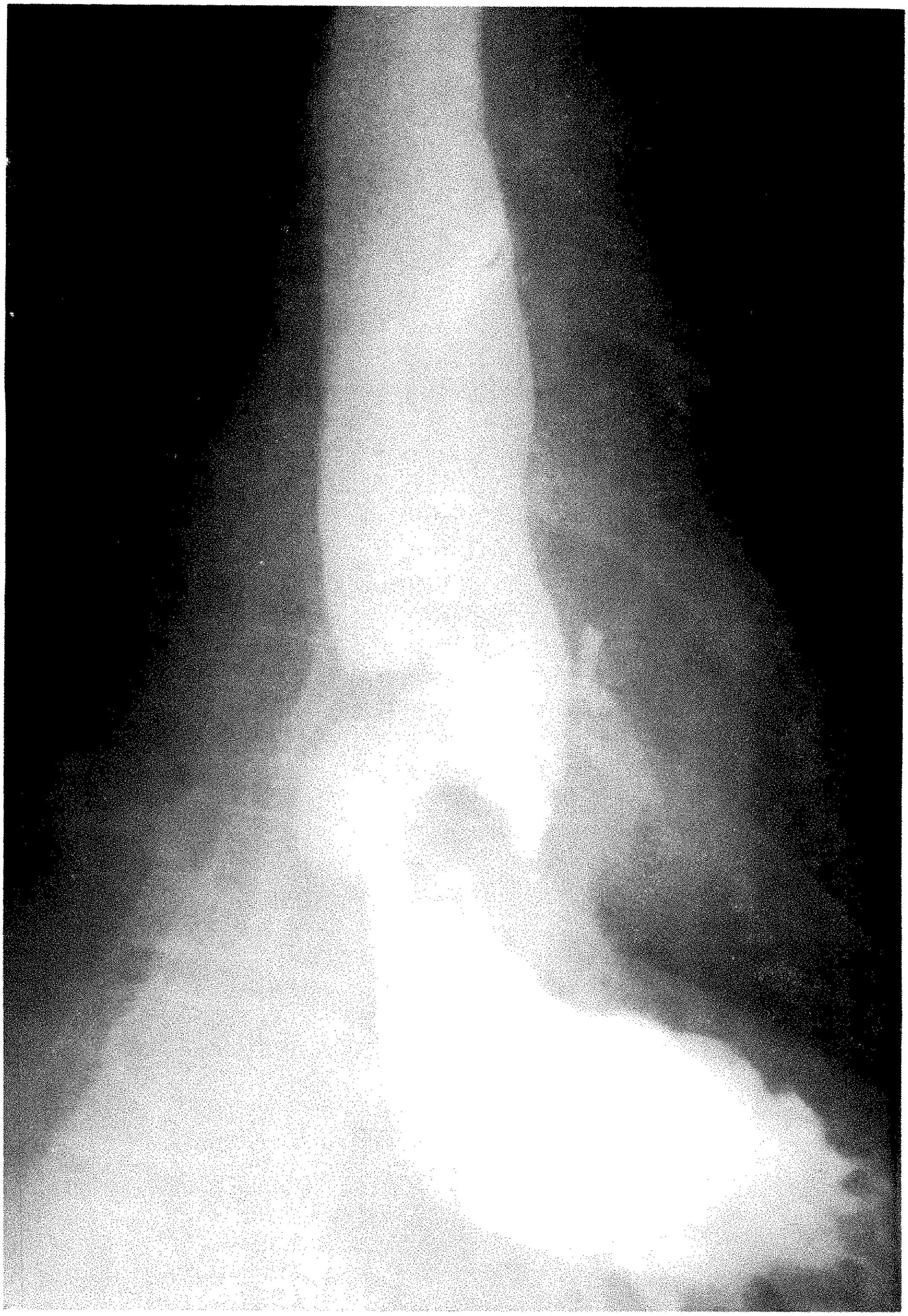

Fig. 4—Esophagram in a patient with Boerhaave's syndrome showing a small amount of contrast material leaking into the mediastinum. The irregularity in the lower end of barium column is due to a hiatus hernia. In adults the leak of contrast material is almost always on the left.

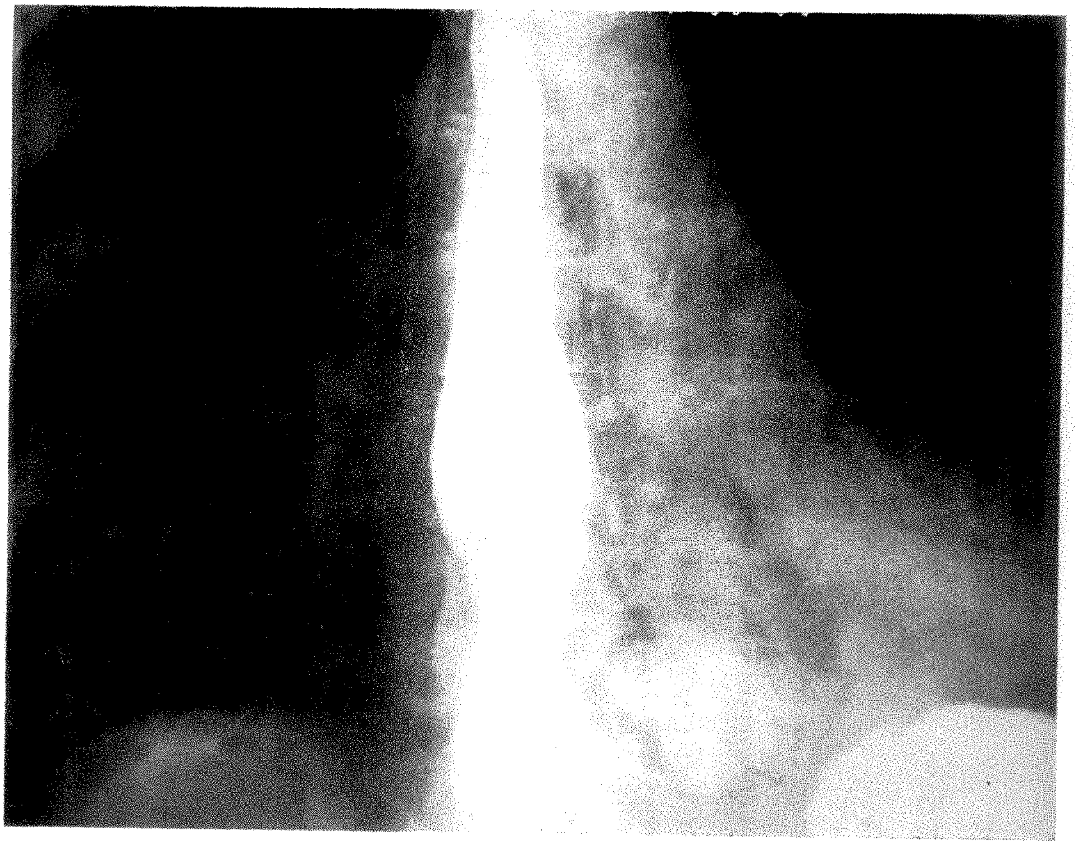

Fig. 5—Esophagram in a patient with Boerhaave's syndrome showing extravasation of contrast material. Note the large amount of air which is also present in the mediastinum.

occur and does not exclude the diagnosis. The amylase may be elevated due to amylase from saliva in the fluid.[23] After the pleura has been ruptured, hydro- or pyopneumothorax results.[24]

Once the diagnosis is considered, confirmation is not difficult by contrast examination of the esophagus. Iodinated water soluble contrast agents,[2, 16, 25] barium and even lipiodol[20] have all been recommended as the contrast medium of choice. In 1975, Vessal, et al instilled barium or water soluble contrast agent with or without bacteria in the mediastinum of cats and found that although the cats with barium developed granulomas, the barium did not serve as a culture medium for the bacteria and the cats did not have any adverse effects.[26] They recommend that an initial study be performed using a water soluble contrast agent but a second examination should be performed with barium if no perforation is identified. Figures 3, 4 and 5 show examples of extravasation of barium in varying degrees in the typical location. The collection of extravasated contrast material may be confused with an epiphrenic diverticulum.[2] The latter is usually right-sided when large[27] and is not associated with pneumomediastinum. The history of recent onset of pain should cause a paraesophageal collection to be viewed with suspicion.

Several authors have stressed the fact that the initial esophagram in a patient with Boerhaave's syndrome may not show extravasation.[2, 24] Consequently, a normal esophagram does not exclude the diagnosis in patients in whom the clinical findings are suggestive. These patients require further barium studies or esophagoscopy. Pneumoperitoneum is strong evidence against Boerhaave's syndrome and suggests rupture of an abdominal viscus. Pneumoperitoneum, however, may occur.[9] Differentiation between spontaneous pneumomediastinum and pneumomediastinum due to Boerhaave's syndrome may be difficult. Spontaneous pneumomediastinum generally occurs in younger people and rarely predominates in the lower mediastinum or is associated with mediastinal fluid.[28] Patients with spontaneous pneumomediastinum may have low grade fever and pain. The pain often subsides when subcutaneous emphysema occurs. It is not associated with pulmonary infiltrates or with pleural effusions. There are many instances, however, when the differentiation requires contrast examination of the esophagus. An esophagram is such an innocuous procedure and spontaneous rupture of the esophagus is potentially so serious, that a contrast study should be performed in any case in which the correct diagnosis is uncertain.

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The Last Page

QUESTIONS IN GASTROENTEROLOGY

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New York, N. Y.

The Last Page appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page,* again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. STUDIES OF THE MUCOSAL FOLDS OF THE GASTRIC ANTRUM REVEAL THAT:
   - A. In the absence of radiologically visible motor activity the folds are circular and oblique in direction.
   - B. During antral contraction the direction of the mucosal folds changes to longitudinal.
   - C. The mucosal folds are static and independent of contraction waves.
   - D. Longitudinal intraluminal mucosal troughs may enhance linear flow of semiliquid intestinal contents.

(Page 147)

2. USING GRAY SCALE ULTRASOUND TO EVALUATE THE PRESENCE OF SURGICAL JAUNDICE IT HAS BEEN NOTED THAT:
   - A. A common bile duct 14 mm. or greater in diameter and/or multiple intrahepatic ducts 4 mm. or greater in diameter suggest obstruction.
   - B. A dilated common duct is not associated with normal intrahepatic ducts.
   - C. A normal common duct can be found in one-third of the cases of obstructive jaundice in which dilated intrahepatic ducts are identified.
   - D. A dilated gallbladder is associated with a malignant process in 90% of cases.

(Page 152)

3. ENDOSCOPIC PAPILLOTOMY AND GALLSTONE REMOVAL:
   - A. Is reserved for high risk but operable patients with choledocholithiasis and with papillary stenosis.
   - B. Has a lower risk than surgical intervention.
   - C. Can lead to perforation, a complication that must be treated surgically.
   - D. Should be limited to centers with well trained and experienced endoscopists.

(Page 159)

4. STUDIES OF BILIARY CHOLESTEROL SATURATION AND CHOLESTEROL GALLSTONE DISSOLUTION REVEAL THAT:
   - A. Phenobarbital decreases biliary cholesterol saturation but the bile does not become cholesterol unsaturated.

---

[*] Assistant Professor of Clinical Medicine, New York University School of Medicine.

B. Phenobarbital enhances chenodeoxycholic acid-induced gallstone dissolution.

C. Lowering of the cholesterol saturation does not dissolve calcified gallstones.

D. Phenobarbital protects against potential chenodeoxycholic hepatotoxicity.

(Page 163)

5. PANCREATIC FUNCTION TESTING BY MEANS OF A SECRETIN TEST REVEALS THAT:

A. Pancreatic secretion is influenced by the age of the individual.

B. Women have lower volume and bicarbonate values when tested with Boots and Vitrum secretin.

C. The peak bicarbonate concentration is the best diagnostic discriminative parameter giving the lowest coefficient of variation.

D. Boots secretin results are not modified by previous sorbitol intraduodenal infusion.

(Page 172)

6. CORRELATIONS OF THE RESULTS OF SECRETIN TESTING, PANCREATIC HISTOLOGY AND ENDOSCOPIC RETROGRADE PANCREATOGRAPHY (ERP) REVEAL THAT:

A. The functional secretory capacity of the pancreas may not correlate well with the histologic structure of the gland.

B. Secretory tests are the most sensitive indicator of chronic pancreatitis although not all cases of chronic pancreatitis will be discovered by this test.

C. Marked fibrosis and acinar atrophy may occur in the absence of any deformity of the ductal system.

D. When secretory tests show low volume output, ERP is necessary to differentiate between malignant ductal obstruction and pancreatic replacement by fibrosis or atrophy.

(Page 180)

7. INTRASPLENIC PANCREATIC PSEUDOCYSTS DEVELOP BY:

A. Direct extension of a pancreatic cyst into the splenic hilum.

B. Digestive effects of pancreatic enzymes on splenic vasculature and parencnyma.

C. Pancreatitis occurring in ectopic intrasplenic pancreatic tissue.

D. Liquefaction of splenic infarcts secondary to thrombosis of the splenic vessels.

(Page 184)

8. OCTANOIC ACID:

A. Will induce a clinical and EEG syndrome resembling hepatic encephalopathy in Rhesus monkeys when infused at levels producing serum concentrations similar to those in comatose cirrhotic patients.

B. Levels are elevated in cirrhotic patients developing hepatic encephalopathy after receiving medium chain triglycerides.

C. Elevation causes a decrease in ATP concentration in the rat cerebral cortex and brain stem.

D. Elevation is caused by incomplete oxidation of palmitate in cirrhotic patients.

(Page 190)

9. EPIPHENOMENA SHARED BY CHRONIC ACTIVE HEPATITIS AND ULCERATIVE COLITIS INCLUDE:

A. High titer peripheral antinuclear antibody titer.

B. Eosinophilia.

V. Hyperglobulinemia.

D. Vasculitis.

(Page 194)

10. RADIATION-INDUCED CHRONIC PROCTOCOLITIS:

A. Appears to be due to an obliterative endarteritis with hyalinization of the connective tissue.

B. After a five-year period may lead to an increased incidence of carcinoma of the colon.

C. Produces symptoms that may mimic those of carcinoma of the colon and rectum.

D. May cause fistulization to the bladder or vagina.

(Page 198)

11. ENDOMETRIOSIS:

A. May cause right lower quadrant abdominal pain associated with menses.

B. Of the appendix can cause inversion and intussusception of the appendix into the cecum.

C. Has an association with uterine leiomyoma.

D. Is not uncommonly associated with mucinous carcinoid tumors.

(Page 200)

12. CROHN'S DISEASE IN CHILDREN AND ADOLESCENTS:

A. Should be suspected when acute abdominal pain is superimposed upon chronic intestinal complaints and abnormalities of growth and development.

B. Is associated with corticosteroid responsive thrombocytopenia.

C. Is often associated with the extraintestinal manifestations of fever, arthritis, arthralgia, digital clubbing, stomatitis, conjunctivitis and *erythema nodosum.*

D. Can be cured by segmental resection of the involved bowel if all draining lymph nodes are carefully removed.

(Page 208)

13. BOERHAAVE'S SYNDROME:

A. Is excluded by the lack of a history of vomiting.

B. Can be suspected if pneumomediastinum is predominant along the lower aspect of the aorta and elevates the parietal pleura from the diaphragm.

C. Is associated with a pleural effusion with a pH less than 6.

D. In infants is associated with a right-sided pleural effusion.

(Page 215)

American Journal of Gastroenterology 69:223-224, 1978
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Vol. 69, No. 2
Printed in the U.S.A.

BOOK REVIEWS FOR GASTROENTEROLOGISTS

World Review of Nutrition and Dietetics: edited by G. H. Bourne. 296 pages, illustrated. S. Karger AG, Basel, Switzerland, 1976. $71.50.

This is no cookbook of recipes but rather a philosophic review of the political and economic problems of nutrition. It attempts to define optimal intake on the basis of the latest data. There are sections related to ecology, the teaching of nutrition, its importance in disease, etc. I am particularly impressed by the sophisticated analysis of the problems and by the attempt to solve them by projections into the future. When will dietetics and nutrition be reintegrated into medicine and gastroenterology? The need is great!

David A. Dreiling, M.D., F.A.C.G.

Spezielle Pathologische Anatomie, Vol. 2, Part 2, Darm und Peritoneum: by H. F. Otto, M.D., M. Wanke, M.D. and J. Zeitlhofer, M.D.; Hernien, by G. Tondury, M.D. 989 pages, illustrated. Springer-Verlag, Berlin, Germany, 1976. Price $196.80.

This, too, is undoubtedly one of the most expensive single volumes I have reviewed. But I must admit it is encyclopedic. The bibliography alone covers 250 pages.

Volume I of the series covered esophagus and stomach; this volume treats small and large intestines, peritoneum and hernia. The latter is merely one appendix to peritoneum and I suspect has been included for completeness. The colored illustrations are beautiful.

When the series is completed, it will stand alone as the "reference". What about English translations?

David A. Dreiling, M.D., F.A.C.G.

Roentgenology of the Gallbladder and Biliary Tract: edited by Benjamin Felson, M.D. 150 pages, illustrated. Grune and Stratton, Inc., New York, N. Y., 1976. Price $14.50.

This book is well written and illustrated by a group of experienced radiologists.

The 22 chapters cover old and recent information; they describe and depict the conventional and modern technics in biliary radiology with clarity and precision.

The complexity of diseases of the biliary system (congenital, calculous and neoplastic) is carefully analyzed and presented to the reader in a concise and meaningful way.

The book is valuable to the radiologists, gastroenterologists and general surgeons interested in biliary disease.

Demetrius Pertsemlidis, M.D., F.A.C.G.

Radiology of the Abdomen: Anatomic Basis, 1st ed.: by Joseph P. Whalen, M.D. 310 pages, illustrated. Lea & Febiger, Philadelphia, Pa., 1976. Price $29.50.

This is just what we needed at last. The correlation of surface and radiologic anatomy of the abdomen with x-ray, sonography and CAT scan. Just go through this text and the gobbledegook of sonography and the Rorschach of CAT scans become crystal clear. Buy this one and learn.

David A. Dreiling, M.D., F.A.C.G.

Physiology of the Digestive Tract (TG-4): by H. W. Davenport. 263 pages, illustrated. Year Book Medical Publishers, Chicago, Ill., 1977. Price $15.95.

Each edition of Davenport's *Physiology of the Digestive Tract* gets thicker but the price is unchanged and the text an utter delight in clarity and conciseness. You could read it in four to five hours and be enlightened and enriched. The 4th edition is a six-year update and very worthwhile.

David A. Dreiling, M.D., F.A.C.G.

Current Topics in Pathology, Vol. 63—Pathology of the Gastro-Intestinal Tract: edited by B. C. Morson, M.D., F.A.C.G. (Hon.) 353 pages, illustrated. Springer-Verlag New York Inc., Secaucus, N. J., 1976. Price $39.40.

Dr. Morson, probably the most eminent gastrointestinal pathologist, maintains the standard of excellence and has chosen wisely the contributors to new and controversial areas, to wit: 1. Early gastric cancer; 2. Pathology of celiac disease; 3. Histologic classification of gastric polyps; 4. Polyps and cancer of the large bowel; 5. Mucin histochemistry of the colon; 6. The precancerous phase of ulcerative colitis; 7. The endocrine cells of the gastrointestinal tract and neoplasms which arise from them; 8. Immunologic aspects of gastrointestinal pathology and 9. Oncofetal and other tumor-associated antigens of the human digestive system.

You may not agree with all that is written but you will admit that this text has got what it takes to bowel you over.

David A. Dreiling, M.D., F.A.C.G.

Operative Endoskopie: by L. Demling, M.D., P. Fruhmorgen, M.D., H. Koch, M.D. and W. Rosch, M.D. 89 pages, illustrated, F. K. Schattauer Verlag GmbH., Stuttgart, Germany, 1976. Price DM 32.

This booklet, written in German, covers a wide spectrum of intraoperative endoscopic procedures. It is of prime interest to the gastroenterologic endoscopist and reflects considerable experience and competence in this area of recent rapid progress.

The authors describe with clarity the technics of polypectomy, biopsy, foreign body extraction, sphincterotomy, coagulation of bleeding vessels and injection of sclerosing agents into bleeding esophageal varices.

The booklet is worth reading by those interested in gastrointestinal endoscopy.

DAVID A. DREILING, M.D., F.A.C.G.

Clinical Gastroenterology, 2nd edition: Howard M. Spiro, M.D., F.A.C.G. 1,289 pages, illustrated. Macmillan Publishing Co., Inc., New York, N. Y., 1977. Price $45.00.

I can see now that my rave review of the 1st edition was justified. Howard has done it again. This is a monumental work reminiscent of the 1st edition of Bockus. As the product of a single author, a unique physician and educator, it presents a broad authorative spectrum of gastroenterology. There has been regrouping, enlargements and new sections, viz apud and pancreatic cholera. At the price and quality, to say nothing of quantity, it's an offer you can't afford to reject.

DAVID A. DREILING, M.D., F.A.C.G.

Current Management of Acute Gastrointestinal Hemorrhage: edited by Teruo Matsumoto, M.D. 256 pages, illustrated. Charles C Thomas, Springfield, Ill., 1977. Price $19.75.

Current Management of Acute Gastrointestinal Hemorrhage is a multiauthored monograph whose contributors are from one institution and apparent collaborators in the multidisciplinary approach to an important and vexing clinical problem. As such, I find the book very rewarding. It presents a coherent clear approach to pathophysiology, diagnosis and treatment of acute gastrointestinal hemorrhage in easily readable type with fine documentation and illustrations. While I may not agree with everything in the text and in this controversial problem, few agree with all, what comes through is "how" we handle this at our institution, our way of doing it. Thus, a clear picture, emerges by reinforcement. I believe this book is of great value to the clinician, the internist and the resident.

DAVID A. DREILING, M.D., F.A.C.G.

CORRECTION

Because of an error in editing, the address of Martin G. Cogan, M.D., which appeared on page 389 of the October, 1977 issue was incorrectly printed. It should have read: Dept. of Med., Div. of Nephrol., 1065 HSE., Univ. of Calif., San Francisco, CA 94143.

The correction has been made in the reprints of the article and we apologize for this error.

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New
Tagamet® Tablets, 300 mg. Injection, 300 mg./2 ml.
brand of
cimetidine

The H_2 Receptor Antagonist

not an anticholinergic
not an antacid

Please see last page for brief summary of prescribing information.

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Tablets,
300 mg.
Injection,
300 mg./2 ml.

ndications / Dosage

- Duodenal Ulcer

  Dosage: 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

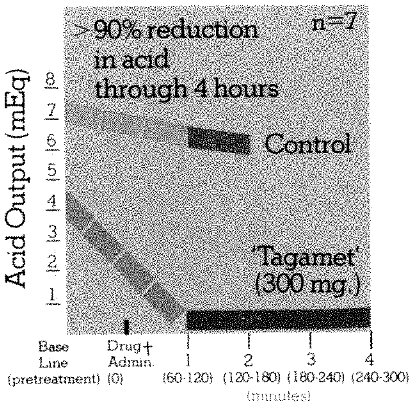
- Pathological Hypersecretory Disorders

  Dosage: 300 mg. four times a day, with meals and at bedtime. In some patients it may be necessary to administer 'Tagamet' 300 mg. doses more frequently (not to exceed 2400 mg. per day) and continue as long as clinically indicated.

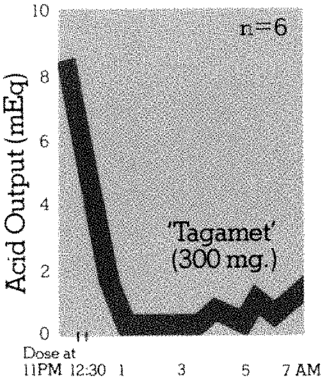
Concomitant antacids should be given as needed for relief of pain.

The 'Tagamet' Effect on Acid Secretion in uodenal Ulcer Patients

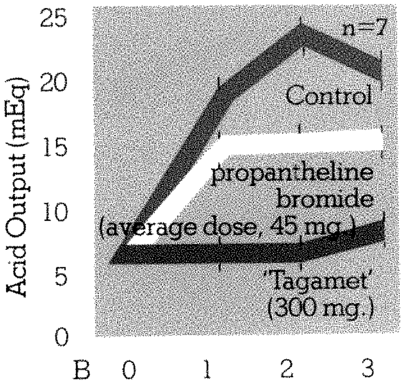
Basal Acid Suppression *



Nocturnal Acid Suppression**



Food-Stimulated Acid Suppression *



Hour Time Periods

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*New England Journal of Medicine, Aug. 21, 1975

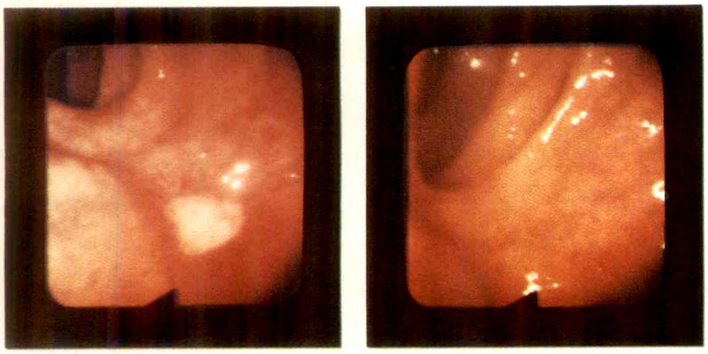
**Data on file, SK&F Medical Dept.

† Broken line indicates decrease from baseline to first measurement after drug administration.

Please see last page for brief summary of prescribing information.

Endoscopically proven Fast, complete ulcer healing

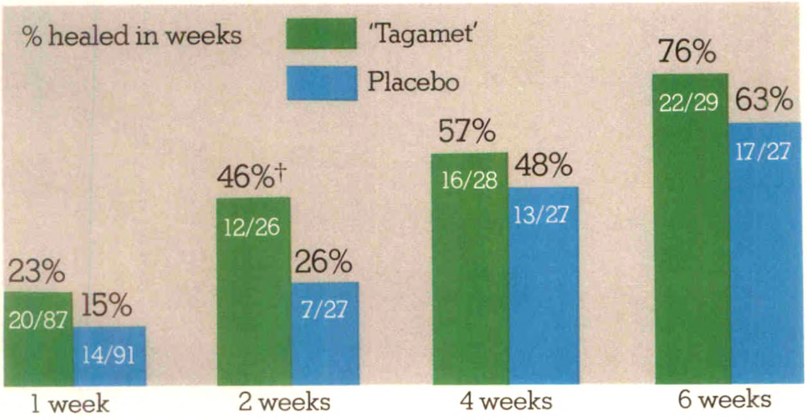
Endoscopic Examination of Duodenal Ulcer Patient on 'Tagamet' 300 mg. q.i.d.



pretreatment **week 2**

- **In a U.S. double-blind study* of patients with endoscopically diagnosed duodenal ulcers, 'Tagamet' (300 mg. four times a day) significantly increased the rate of healing vs. placebo at two weeks, proven endoscopically.**

Heal Rates in Duodenal Ulcer Outpatients



Effective Symptom Relief

- **In the same U.S. double-blind study,* global efficacy ratings of complete or marked relief were reported in 80%‡ of the patients on 'Tagamet' vs. 59% for placebo.**

*Data on file, SK&F Medical Dept.
(all patients were permitted p.r.n. antacids for relief of pain)

†$p<0.05$

‡$p<0.01$

New
Tagamet®
brand of
cimetidine

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Tagamet®
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cimetidine

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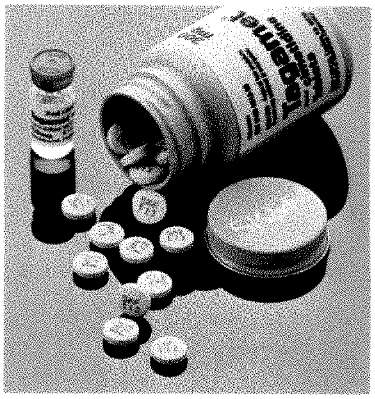

- **Inhibits gastric acid secretion produced by all common stimulants:**
  - **food, histamine, vagal, pentagastrin, caffeine**
- **Promotes rapid ulcer healing**
- **Provides effective symptom relief**
- **Well tolerated**
  - **based on clinical trials, the following are the most frequently reported adverse reactions: diarrhea; dizziness; muscular pain; rash; mild gynecomastia**

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of neutropenia have been reported, but no causal relationship could be established. Small, regularly observed, reversible increases in plasma creatinine and some increases in serum transaminase have been reported.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials in packages of 10.

Date of issuance Sept. 1977

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COMPOSITION: Each 60 ml. unit contains Hydrocortisone, 100 mg. in an aqueous solution of carboxypolymethylene, polysorbate 80, and methylparaben, 0.18% as a preservative.
INDICATIONS: Adjunctive therapy in ulcerative colitis; especially distal ulcerative proctitis, proctosigmoiditis, left-sided colitis; proved useful also in some cases involving transverse and ascending colons.
CONTRAINDICATIONS: Systemic fungal infections; recent ileocolostomy.
WARNINGS: In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.

Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
ADVERSE REACTIONS: Local pain or burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:

Fluid and Electrolyte Disturbances: Sodium retention, fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
HOW SUPPLIED: Single-dose 60-cc. bottles, in packages of 1 or 7, with instructions for patients.

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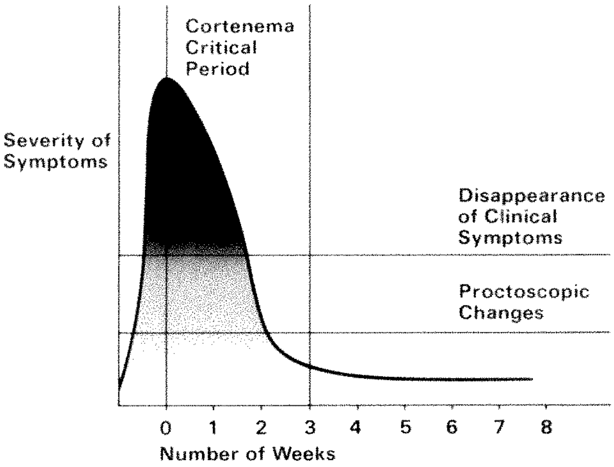

Once a diagnosis is established, Cortenema often is the only medication required for treatment of mild to moderate distal ulcerative colitis, characterized by rectal bleeding, stool abnormality (diarrhea or constipation), and diffuse mucosal ulceration and friability limited to the rectum or rectosigmoid colon.

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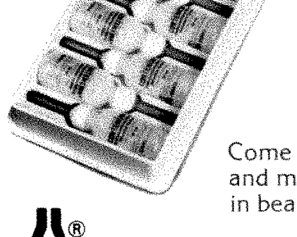

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See page opposite for brief summary.

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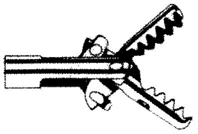
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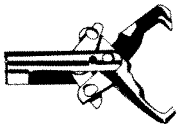
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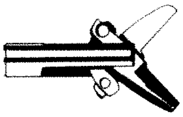
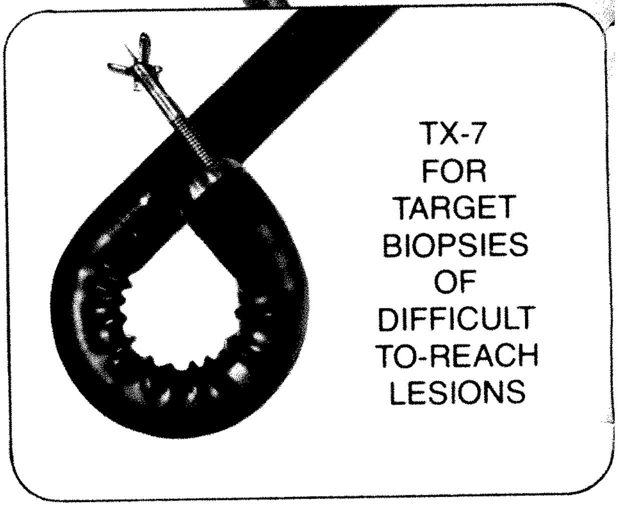

7046A Scissors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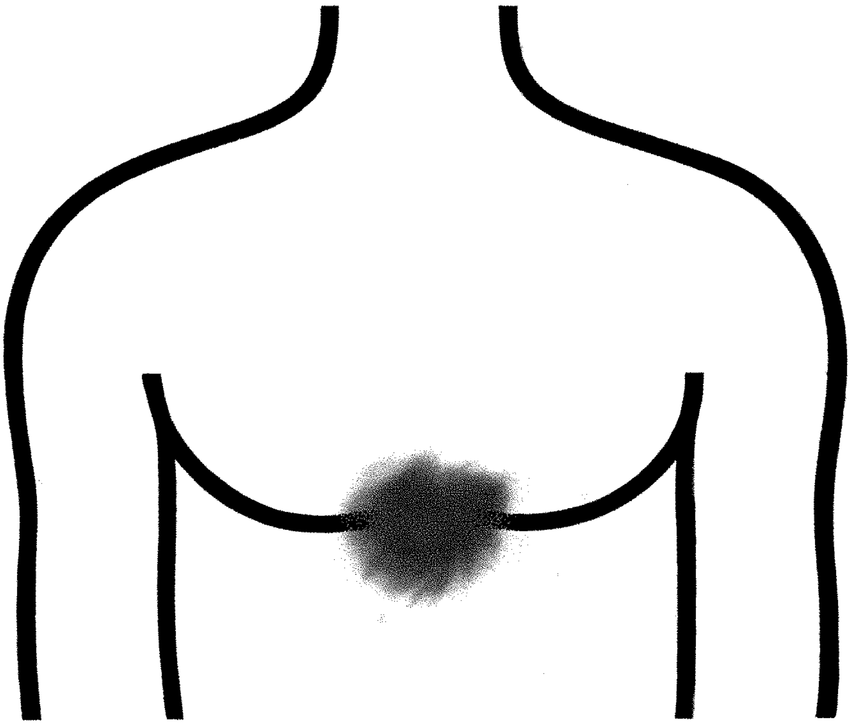

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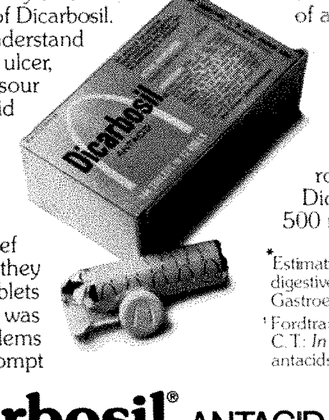

*Estimated annual economic loss from digestive disease, cited by Almy, T.P.: Editorial, Gastroenterology 66:152-6 (Jan.) 1974.

[1] Fordtran, J.S.; Morawski, S.G., and Richardson, C.T.: *In vivo* and *in vitro* evaluation of liquid antacids, New Eng. J. Med. 288:923-28, 1973.

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Fulminant Hepatic Failure*

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and
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New York, NY

A conference on Fulminant Hepatic Failure (FHF), co-sponsored by the National Institute of Arthritis, Metabolism and Digestive Diseases and the John E. Fogarty International Center of the National Institutes of Health, was held at the NIH, Bethesda, MD on 7-9 February 1977. This meeting served to update information presented at an International Symposium on Artificial Support Systems for Acute Hepatic Failure held in London in 1975. In addition, it reviewed the current knowledge of the physiology, pathogenesis, pathophysiology and treatment of fulminant hepatic failure.

There were 14 sessions titled as follows:

. . . . Liver Cell Necrosis and Organelle Dysfunction
. . . . Clinical Biochemistry of Fulminant Hepatic Failure
. . . . The Brain in Fulminant Hepatic Failure
. . . . Cerebral Edema
. . . . Other Organ Dysfunction in Fulminant Hepatic Failure
. . . . Etiology of Fulminant Hepatic Failure
. . . . Assessment and Prognosis
. . . . Hepatic Regeneration: Normal Regulation, Abnormalities
. . . . Causes of Death in Fulminant Hepatic Failure
. . . . Treatment of Fulminant Hepatic Failure
. . . . Artificial Hepatic Support
. . . . Experimental Approaches to the Pathophysiology of FHF
. . . . Importance of Controlled Trials
. . . . A Coherent Approach to Fulminant Hepatic Failure and Liver Support: Lessons from the Chronic Uremia Program

The United States and ten foreign countries were represented by the 60 speakers who included biochemists, pathologists, neurologists, neurophysiologists, epidemiologists and biomedical engineers in addition to the hepatologists. Each paper or group of papers was followed by ample discussion time to promote cross-discipline interaction.

Co-sponsored by the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD) and the John E. Fogarty International Center for Advanced Study in the Health Sciences.

* Annotated Abstracts of a Workshop Held at The National Institutes of Health, Bethesda, MD, 7-9 February 1977.

The following persons gave presentations and/or chaired sessions at the conference:

George M. Abouna, Provident Professional Building, Calgary, Canada

Jean-Pierre Benhamou, Hôpital Beaujon, Clinchy, France

Paul D. Berk, NIAMDD, Bethesda, MD

Pierre Berthelot, Hôpital Henri Mondor, Creteil, France

Julien F. Biebuyck, University of Cape Town Medical School, Cape Town, South Africa

Laurence M. Blendis, Toronto General Hospital, Toronto, Canada

Bennett L. Blitzer, NIAMDD, Bethesda, MD

Joseph R. Bloomer, Yale University, New Haven, CT

Gorig Brunner, Medizinsche Universitätsklinik, Göttingen, W. Germany

Nancy L. R. Bücher, Massachusetts General Hospital, Boston, MA

Benjamin T. Burton, NIAMDD, Bethesda, MD

Thomas C. Chalmers, Mount Sinai Medical Center, New York, NY

Thomas Ming Swi Chang, McGill University, Montreal, Canada

Burton Combes, University of Texas, Dallas, TX

Robert L. Dedrick, Division Research Services, NIH, Bethesda, MD

Ennio Denti, Sorin Biomedica, Saluggia, Italy

Thomas E. Duffy, Cornell University, New York, NY

Josef E. Fischer, Massachusetts General Hospital, Boston, MA

Robert A. Fishman, University of California, San Francisco, CA

Peter T. Flue, St. Georges Hospital Medical School, London England

Peter Fürst, St. Eriks Hospital, Stockholm, Sweden

John T. Galambos, Emory University, Atlanta, GA

Carl A. Goresky, Montreal General Hospital, Montreal, Canada

Lee W. Henderson, Veterans Administration Hospital, San Diego, CA

E. Anthony Jones, NIAMDD, Bethesda, MD

Theodor Kolobow, NHLBI, Bethesda, MD

Milo D. Leavitt, Jr., Fogarty International Center, NIH, Bethesda, MD

Heinrich Liehr, University of Würzburg, Würzburg, W. Germany

Bruce MacGillivray, Royal Free Hospital, London, England

Roshan Maini, University Strathclyde, Glasgow, Scotland

James W. Mosley, University of Southern California, Los Angeles, CA

Yukihiko Nose, Cleveland Clinic Foundation, Cleveland OH

V. Nusinovici, Hôpital Saint Antôine, Paris, France

Pierre Opolon, Hôpital Saint Antôine, Paris, France

John C. Partin, Children's Hospital, Cincinnati, OH

Paul H. Plotz, NIAMDD, Bethesda, MD

Fred Plum, Cornell University, New York, NY

Hans Popper, Mount Sinai School of Medicine, New York, NY

Rudolph Preisig, University Berne, Berne, Switzerland

Allan E. Redeker, University of Southern California, Los Angeles, CA

Telfer B. Reynolds, University of Southern California, Los Angeles, CA

Bernard Rueff, Hôpital Beaujon, Clinchy, France

Stuart J. Saunders, University of Cape Town, Cape Town, South Africa

André Sausse, Rhone-Poulenc-Industries, Paris, France

Fenton Schaffner, Mount Sinai School of Medicine, New York, NY
Bruce Scharschmidt, University of California, San Francisco, CA
Steven Schenker, Vanderbilt University and VAH, Nashville, TN
Jacques Scotto, INSERM Hôpital de Bicêtre, France
Sheila Sherlock, Royal Free Hospital, London, England
Arnold L. Smith, Children's Hospital, Boston, MA
Philip J. Snodgrass, Indiana University and VAH, Indianapolis, IN
Nigel N. Stanley, Central Middlesex Hospital, London, England
David S. Terman, Baylor College of Medicine, Houston, TX
Paul F. Teychenne, NINDS, Bethesda, MD
Peter Trewby, King's College Hospital, London, England
Niels Tygstrup, University Hospital, Copenhagen, Denmark
Athol J. Ware, University of Texas, Dallas, TX
G. Donald Whedon, NIAMDD, Bethesda, MD
Roger Williams, Kings' College Hospital, London, England
Carl F. W. Wolf, New York Blood Center, New York, NY
Leslie Zieve, University of Minnesota, Minneapolis, MN
Hyman J. Zimmerman, George Washington University and VAH, Washington, DC

Acute, fulminant hepatic failure (FHF) with coma is one of the most dramatic situations with which the clinical hepatologist is presented. It is also the most frustrating, in that death results in the large majority of instances, despite enormous effort by the medical and nursing staffs. While there is an impression that improved intensive care has led to some increase in survival rate, no actual data support this contention and 80-90% of such patients whose disease has progressed to stage IV coma die.

The continuing bleak prognosis for patients with FHF stands in sharp contrast to current results in uremia, in which dramatic improvements in survival have resulted from continuously improving "artificial kidney" devices.[1, 2] Success with these devices has led hepatologists to explore analogous hepatic support devices in FHF. The first systematic clinical investigation of an artificial hepatic support system was begun at Kings College Hospital, London, in 1973. The results with this system served as the focal point for an International Symposium on Artificial Support Systems for Acute Hepatic Failure.[3] In view of both the apparent success achieved and the exceptional level of interest among workers in the field, it was agreed that a follow-up symposium should be planned. The resulting International Symposium on Fulminant Hepatic Failure held at the National Institutes of Health, Bethesda, Maryland, on 7-9 February 1977 was the culmination of those plans. Its purpose was to review current knowledge of physiology, pathogenesis, pathophysiology and treatment of fulminant hepatic failure. An attempt was made to include biochemists, pathologists, neurologists, neurophysiologists, epidemiologists and biomedical engineers in the program to the greatest possible extent, in order to maximize the areas of expertise brought to bear on the problems. Several papers were devoted to morphologic, pathogenetic and therapeutic aspects of Reye's syndrome because of the light that they shed on analogous problems in more typical FHF. The following is an attempt to summarize the salient facts presented at this meeting. It consists of edited versions of the abstracts submitted by the speakers, as well as notes on the presentations and discussions recorded by members of the conference organizing committee. The bibliography was solicited from the speakers and represents a compendium of the current literature in the field.

MORPHOLOGIC FEATURES AND PATHOGENESIS OF FHF

The session chaired by Hans Popper, M.D., F.A.C.G. (Hon.) of the Mount Sinai School of Medicine of the City University of New York, was opened by Dr. Popper's presentation on Mechanisms of Liver Cell Necrosis.[4-8] The clinical syndrome of FHF may result either from cell necrosis or from organelle dysfunction in living liver cells. Hepatocytic necrosis becomes functionally significant only if it involves the major part of the organ. Organelle dysfunction, on the other hand, is the basis of the functional hepatic deficit in most liver diseases, including some cases of FHF in which the extent of observed necrosis is insufficient to account for the degree of functional deficit. Massive steatosis in the large livers of alcoholic women represents an example in which FHF occurs virtually without necrosis. Reye's syndrome, generally considered to be a similar example, is now recognized as being more complex, due to profound metabolic disturbances in many organs beside the liver. In FHF due to necrosis, the mechanism of death of liver cells remains poorly understood, except when associated with anoxia. Cell death appears to be an active sequential process associated with specific molecular alterations. The initial target, however, remains in dispute and at present there is no known intervention which can halt or reverse the process of cell death, once initiated. Considerable evidence points to injury of cell membranes, including intracellular organelle membranes, followed by abnormal influxes of calcium, as critical events in cell death. Membrane injury may result either from chemical mechanisms or, in the case of hepatocytes containing HBsAg in their membrane, from immunologic events.

Morphologic Findings in Fatal or Severe Viral Hepatitis[9-12] were described by Jacques M. Scotto, M.D., Hôpital de Bicêtre, France, based on experience with 104 liver biopsies obtained from 78 patients with FHF. The uniform histologic features were qualitatively similar but quantitatively much more severe than in viral hepatitis without FHF. Steatosis was frequent even in the absence of corticosteroid treatment. As previously reported, stereological quantitation of viable hepatocytes correlated well with prognosis, especially if it was possible to compare the hepatocyte volume fraction in two or more consecutive biopsies. Forty-five biopsy specimens from 35 patients were examined by electron microscopy. There was a statistically significant relationship between the presence of glycogen bodies and ultimate recovery. Granular, fibrillar, nonmembrane bound inclusions were another common feature. Typical 22 μm. viral particles, principally intranuclear, were observed in only one case. Other viral-like particles were seen in some additional patients, but their viral nature could not be confirmed.

John T. Galambos, M.D., F.A.C.G., Emory University School of Medicine, Atlanta, GA, described the development of Chronic Liver Disease after FHF, which was noted in three of 15 patients whose initial biopsies were obtained shortly after recovery of consciousness. Sequential biopsies revealed the development of asymptomatic fibrosis, cirrhosis and mild chronic hepatitis in one patient each. These data are in contrast to previous reports suggesting that complete histologic recovery usually occurs in surviving patients.[13-15]

John C. Partin, M.D., Children's Hospital Research Foundation, Cincinnati, OH, in discussing Mitochondrial Ultrastructure in Reye's Syndrome[16-20] emphasized that Reye's syndrome has been considered in the past as an example of FHF due to organelle dysfunction of hepatocytes without necrosis. He recommended reconsideration of this concept on the basis of electron microscopic study of liver biopsies obtained from 75 cases of Reye's syndrome and 25 patients with some form of acute encephalopathy associated with abnormal liver function but without Reye's syndrome. In the Reye's syndrome group, biopsies obtained within the first 36-48 hours of encephalopathy show little inflammation or necrosis. The striking ultrastructural lesion is panlobular involvement of hepatocyte mitochondria, with total loss of dense bodies, expansion of the matrix space and separation of matrix material into coarse, beaded strands. The changes were similar from cell to cell and all mitochondria in a cell were equally involved. In severe cases, the changes may be associated with rupture of the outer mitochondrial membrane. In osmium-fixed tissues, marked mitochondrial pleomorphism into ameboid shapes was apparent. This was less apparent in glutaraldehyde-fixed material which, however, is better to establish glycogen depletion, a feature which correlates with severity. Biopsies obtained on or after the fourth day may not show these features to a degree sufficient to allow a positive ultrastructural diagnosis. These mitochondrial changes were not seen in children with encephalopathy associated with a variety of other forms of hereditary and/or acquired liver disease.

Of particular interest was the observation, in three patients subjected to craniectomy for cerebral edema, that similar mitochondrial changes occurred in the majority of cortical neurons, although not in brain supporting cells or vascular endothelium. Mild mitochondrial lesions were also found in a proportion of skeletal muscle biopsies examined. Exchange transfusion and glucose infusion usually rapidly reversed the hepatic lesion even if the patient went on to die a cerebral death. Hence, it is no longer established that the encephalopathy in Reye's syndrome is secondary to the hepatic injury, but rather is a manifestation of a more generalized mitochondrial injury.

In a further consideration of Reye's syndrome, Philip J. Snodgrass, M.D., Indiana University School of Medicine, Indianapolis, IN, described the nature of the Mitochondrial Dysfunction in Reye's Syndrome.[21-25] The severity of the early, transient hyperammonemia correlates with survival and may play a role in the encephalopathy. In 90% of cases studied, the hyperammonemia was associated with a reduced activity of hepatic ornithine transcarbamylase and in 60%, with a reduction of carbamyl phosphate synthetase. These two enzymes in the hepatic urea cycle are mitochondrial, while the activity of the three cytoplasmic urea cycle enzymes are normal. Hence, these findings support both the ultrastructural and histochemical evidence of a specific mitochondrial lesion in Reye's syndrome reported previously. Studies of Kms, pH optima and heat lability do not support the concept that mutant enzymes make some children genetically susceptible to Reye's syndrome. The extent to which other mitochondrial functions besides urea metabolism are affected is unclear. Although impairment of oxidative phosphorylation has been suggested, the ATP content of Reye's syndrome liver homogenates is normal. Furthermore, although an altered appearance of mitochondria has been observed in organs other than the liver, functional abnormalities in these organs have not been documented. Hence, it remains unclear whether the encephalopathy and cerebral edema in Reye's syndrome are secondary to hepatic dysfunction, or due to a common induced injury to mitochondria in a variety of tissues besides the liver.

Clinical Biochemical Findings in FHF

Pierre Berthelet, M.D., Hôpital Henri Mondor, Creteil, France, chaired this session. Leslie Zieve, M.D., Veteran's Administration Hospital, Minneapolis, MN, stressed the Role of Mercaptans and of Synergism among Toxic Factors in FHF.[26-30] Many biochemical disturbances occur in FHF but it is unclear which, if any, is responsible for coma. Mercaptans are thioalcohols formed by bacterial action in the gut from methionine and ordinarily cleared from portal blood almost completely by the liver. Like ammonium salts and fatty acids, administration of mercaptans such as methanethiol can induce reversible coma in experimental animals. Elevated blood levels are observed in both animals and patients with chronic hepatic encephalopathy. In experimental animals, methanethiol, NH_4 and fatty acids each potentiate the coma-producing effects of the other two. While the blood level of each of these compounds is elevated following the production of acute, massive hepatic necrosis in the rat, the level of each is far below that required to produce coma in normal rats from administration of a single compound. When, however, normal rats are given methanethiol. NH_4 and fatty acids in a combination which results in respective blood levels similar to those observed in rats with massive hepatic necrosis, the normal rats become comatose. Thus, the encephalopathy in experimental FHF can be explained by the synergistic interaction of those three classes of toxic materials, without invoking a role for other hypothetical toxins.

Josef E. Fischer, M.D., Department of Surgery, Massachusetts General Hospital, Boston, MA, spoke about Blood Amino Acids and the Therapeutic Implications of Different Patterns in Acute and Chronic Liver Disease.[31-35] The metabolism and synthesis of brain neurotransmitters is in part dependent on relationships between specific groups of amino acids in both the central nervous system and the plasma. Abnormalities in plasma amino acid patterns have been known for some time in both animals and patients with hepatic encephalopathy. Two distinct patterns of amino acid abnormalities in patients with hepatic encephalopathy are now recognized: 1. In patients with exacerbations of chronic liver disease leading to encephalopathy, the characteristic pattern is an elevation in plasma phenylalanine, tyrosine, free (but not necessarily total) tryptophan and to some extent methionine, glutamate and aspartate. The branched chain amino acids valine, leucine and isoleucine are generally reduced. The principal source of the elevated plasma amino acids is believed to be skeletal muscle and, to a much lesser extent, liver. 2. In patients with FHF, all amino acids are elevated with the exception of the branched chain compounds, which are typically normal or slightly decreased. In some animal models of FHF, branched chain amino acids are slightly elevated but to a much lesser extent than aromatic amino acids. The source of the plasma amino acids in this setting is the necrosing liver.

In dogs with portacaval shunts and patients with decompensated chronic liver disease, infusions of a glucose/amino acid mixture high in branched chain and low in aromatic amino acids rapidly reverses catabolism and promotes arousal, even when up to 120 gm./24 hr. of amino acids are administered. Thus, a synthetic amino acid diet of similar formulation may be well tolerated by patients with chronic liver disease or those with postshunt encephalopathy. In contrast, the coma and the pattern of plasma amino acid abnormalities in

FHF are not amenable to correction by infusion therapy alone but must be coupled with some form of artificial hepatic support system (*vide infra*).

Marsha Morgan, M.D., Royal Free Hospital, London, England, commented that plasma amino acid concentration patterns in cirrhotic patients without encephalopathy were, in general, similar to those reported by Fischer for encephalopathic chronic liver disease.

Rudolf Preisig, M.D., Department of Clinical Pharmacology, University of Berne, Switzerland, presented new observations on the Biliary Transport and Cholestatic Effect of Aminoacids.[36-40] Little information has been available on the biliary excretion of amino acids. Bile: serum amino acid concentration ratios were determined in anesthetized rats. Ratios were invariably < 1.0 for basic amino acids, > 1.0 for acidic amino acids (3.2 and 5.7 for glutamate and aspartate, respectively) and also > 1.0 for all neutral amino acids except alanine. Since biliary concentrations of cysteine were much greater than those of serum, its biliary transport must differ from that in kidney and gut, where it shares a common transport mechanism with lysine, arginine and ornithine.

When the *in situ* perfused rat liver was infused with either ^{14}C-methionine or ^{14}C-cycloleucine (a nonmetabolized amino acid), transport maxima of 38.6 ± 6 (S.D.) and 33.5 ± 5 μm./min./gm. liver were calculated. These values are similar to the Tm for BSP but only 15-20% of that for taurocholate. Bile salt infusions augmented amino acid transport maxima by up to three-fold.

During the amino acid infusions, maximal biliary amino acid concentration was followed in each instance by a progressive decrease in bile flow and virtual abolition of the bile salt independent fraction. There was an inverse correlation between perfusate amino acid concentration and resulting bile flow. These phenomena were reproducible in the intact rat. Amino acid induced cholestasis may therefore be clinically significant with high plasma concentrations of some amino acids. The cholestatic syndrome occurring in children following intravenous administration of protein hydrolysates or amino acid mixture is one example. In FHF, this phenomenon may inhibit excretion of toxic compounds by residual functioning tissue, thereby contributing to perpetuation of the lesion.

Stuart J. Saunders, M.D., Department of Medicine, University of Capetown, Union of South Africa, followed by describing Influence of Amino Acids on Formation of New Liver Cells and Restoration of Function.[41-44] In view of the elevated plasma amino acid concentrations in hepatic failure and the suggested use of amino acid infusions for therapy in this condition, the effect of amino acid infusions on hepatic function (albumin synthesis) and regeneration (^{14}C-thymidine incorporation into DNA) was investigated in rats following partial hepatectomy. Following surgery, either a mixture of 11 essential amino acids, branched chain amino acids alone or the keto analogs of the branched chain amino acids all produced a significant increase in hepatic albumin synthesis as measured *in vivo* by the ^{14}C-carbonate technic. By contrast, mixtures of the 11 essential amino acids significantly inhibited incorporation of precursor into DNA. Thus, administration of amino acids in a situation of rapid regeneration may stimulate synthesis of export protein, but inhibit the capacity of the hepatocytes to regenerate.

Ligandinemia as an Index of Liver Necrosis[45-47] was another subject also discussed by Stuart J. Saunders, M.D. Ligandin constitutes 5% of hepatic cytosol proteins and therefore considerable release into the circulation could be expected during liver cell necrosis. Using a new radioimmunoassay, plasma ligandin levels rose to 12 times normal by 3 hours and 370 times normal by 24 hours after intragastric administration of CCl_4 to rats. SGOT increased to only 1.3 times normal at 3 hours but reached 140 times normal at 24 hours. Acute bile duct ligation in the rat increased ligandin to 3.5 times normal at 12 hours with normal values by 24 hours, whereas SGOT was elevated to roughly seven times normal at both times measured. Intravenously administered ligandin was rapidly cleared from plasma with fractional removal rates of 0.7-5.3/hr. Thus, the massive release and rapid clearance of ligandin make measurements of ligandinemia a potentially valuable measure of on-going liver cell necrosis.

Serum Enzyme Activities in the Differential Diagnosis of FHF[48-54] were stressed by Hyman J. Zimmerman, M.D., Veterans Administration Hospital, Washington, DC. Clinical FHF is seen mainly in association with three distinctive histologic pictures: acute massive necrosis (viral or toxic hepatitis), acute steatosis (steatosis of pregnancy, acute toxic steatosis following intravenous high doses of tetracycline, Reye's syndrome) and steatonecrosis (alcoholic hepatitis). Certain basic serum biochemical tests may provide a useful clue to the underlying lesion. In particular, hepatic failure due to steatonecrosis is associated with much more modest elevations of SGOT ($<$ 300 K-A units) and SGPT (often normal, almost invariably $<$ 100 K-A units) than the other two lesions. Thus, in acute massive necrosis with hepatic failure, both SGOT and SGPT are, at some point, in the range of 1,000-4,000 K-A units, whereas in acute steatosis, elevations of these enzyme activities tend to be somewhat less (300-2,000 K-A units). Jaundice tends to be absent or mild in acute steatosis but deep in acute necrosis with hepatic failure if the patient survives beyond a few days. Moreover, in acute steatosis due to Reye's syndrome, there may be elevated CPK values secondary to muscle or myocardial injury. No data suggest that measurements of serum activities of hepatic mitochondrial enzymes such as glutarate dehydrogenase or the mitochondrial fraction of GOT are of value in the diagnosis of Reye's syndrome.

Peter Fürst, M.D., St. Erik's Hospital, Stockholm, Sweden, discussed Measurement of Intracellular Metabolites in Hepatic Failure.[55-57] In severely ill patients, fundamental metabolic functions such as energy generation, amino acid metabolism and transmembrane transport may be impaired, as they are in hepatic failure. These intracellular processes can be evaluated by studies performed on muscle tissue obtained by percutaneous needle biopsy. Previous investigations of intracellular pH, electrolytes, cyclic nucleotides, amino acid and energy metabolism have been carried out in uremia and a variety of other catabolic states. Frequently, the patterns of abnormalities observed are fairly specific for the particular catabolic state. For example, the patterns of intracellular free amino acids in uremia differ from those seen in postoperative or starving patients. In preliminary observations in patients with hepatic failure, the changes observed in intracellular amino acid pattern were different from those reported in plasma by Fisher. Patients in hepatic failure also exhibit low muscle ATP and low energy charge potential, features more generally characteristic of catabolic states and "sick cells". Since these preliminary observations reveal intracellular metabolic abnormalities different from those observed merely in plasma, more extensive studies of intracellular metabolism in FHF may provide important insights into various aspects of the syndrome.

The preceding speaker continued with a presentation entitled Screening of Biologic Fluids for Abnormal Metabolites: Lessons from the Study of Uremia.[58-59] Numerous substances accumulate in the blood of patients with uremia and FHF. In order to conclude that a compound is toxic, certain criteria should be met. These include: 1. structural identification; 2. methods for its quantitation in biologic fluids; 3. higher plasma levels in uremic or FHF patients than in other patients as controls; 4. correlation of high concentration with specific clinical symptoms and 5. reproduction of toxic effects in animals or *in vitro* systems at concentrations comparable to those observed clinically. As a result of extensive experience with dialysis in uremia, putative uremic toxins are classified as "small molecules" (MW < 500, highly dialyzable through conventional dialysis membranes); "middle molecules" (MW 500-5,000, relatively poorly dialyzable through conventional membranes but more readily removed through special, porous membranes); and "big molecules" (MW $> 5,000$, practically nondialyzable). A similar classification may be useful in FHF.

Most studies of toxicology in these conditions have focused on a single compound (e.g. urea, creatinine in uremia; ammonia in FHF). Recently technics have been developed for screening biologic fluids such as uremic plasma by combinations of ion exchange chromatography, solvent extraction, ion pair extraction, ultra filtration, gel filtration, etc. Separation, concentration and structural determination of single compounds or groups of compounds may require only a few or numerous steps, including derivative formation for gas chromatography or coupled, computerized mass spectrometry. This approach has identified many potential toxins in uremic patients and may be applicable as well in FHF. Ultimate establishment of toxicity awaits, animal or in vitro demonstration of such effects. The application of such technics in uremia has permitted the identification of specific uremic middle molecules which include a peptide (designated peak 7c) of clycine, glutamic acid, leucine, phenylalanine, tyrosine and histidine, present in concentrations of up to 7 μg./ml. in uremic plasma but absent from normal plasma. Studies are currently being conducted to correlate concentration with clinical features as well as to establish its potential toxicity in *in vitro* studies (this compound, for example, markedly inhibits blast transformation, possibly related to the impaired immune responses in uremic patients). While such complex, systematic screening procedures have not yet been applied in FHF, they may prove valuable in identifying currently unsuspected compounds which require removal by artificial hepatic support devices.

THE BRAIN IN FHF

This session was moderated by Robert Fishman, M.D., University of California, School of Medicine, San Francisco, CA. Nigel Stanley, M.D., The Middlesex Hospital, London, England, spoke about Sensitivity of Ventilation, Cerebral Circulation and Cerebral Metabolism to the Blood Gas State in FHF.[60-62] He stressed that FHF is often accompanied by severe hypoxia and hypocapnia and decreased cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRo_2$). Effects of abnormal blood gases were therefore studied by measuring changes in ventilation, CBF and $CMRo_2$ evoked by breathing hypoxic or CO_2 enriched gas mixtures in goats with acute hepatic necrosis induced by carbon tetrachloride. During hepatic failure the goats became hypocapnic; their CBF fell by 30% and $CMRo_2$ by 22%. Even more striking were decreases in the ventilatory and CBF responses to CO_2. Reversing their hypocapnia by CO_2 breathing caused a further decrease in $CMRo_2$. The ventilatory response to brief periods of hypoxia was increased by 61%, suggesting heightened sensitivity of the peripheral chemoreceptors. The ventilatory increment was not maintained, however, in prolonged hypoxia, consistent with hypoxic depression of the respiratory centers. The CBF response to hypoxia was decreased by 61%. There was also a further reduction in $CMRo_2$ at arterial and cerebral venous O_2 tensions much higher than their usual critical threshold values for producing hypoxic $CMRo_2$ depression in health. The findings suggest that the usual hypocapnia in FHF is probably beneficial, but that moderate hypoxia may be detrimental to cerebral function. Moreover, there may be impairment of the homeostatic mechanisms, involving both ventilation and the cerebral circulation, that normally buffer the brain tissue against changes in the arterial gas tensions.

The Current Status of Alpha-ketoglutaramate in the Cerebrospinal Fluid: Dynamic Metabolism of $^{13}NH_3$ in Man[63-65] was discussed by Fred Plum, M.D., New York Hospital-Cornell Medical Center, New York, NY. In 1974, Vergara, et al, described the previously unrecognized compound, α-ketoglutaramate (α-KGM) in the cerebrospinal fluid of controls and patients with liver disease. Elevated α-KGM levels in CSF correlated more closely with hepatic encephalopathy than did either ammonia or glutamine levels. Physiological and biochemical studies of the effects of α-KGM, however, have indicated that the compound neither alters cerebral cortical synaptic activity nor impairs the metabolism of cerebral tissue slices. Thus, α-KGM is a nontoxic by-product of cerebral ammonia metabolism rather than a causative factor in hepatic encephalopathy. Levels of α-KGM are not elevated in Reye's syndrome. In collaboration with associates in the Biophysics Laboratory of the Memorial Sloan-Kettering Cancer Center, carrier free $^{13}NH_4Cl$ has been synthesized and tracer doses injected intravenously to five normal subjects and 15 patients with liver disease, in whom arterial ammonia $[NH_3]_a$ ranged from 52-264 μM. Ammonia was cleared from blood at a high rate. $^{13}NH_3$ entered brain, liver and muscle freely and organ activity remained maximal after the specific activity of arterial NH_3 fell to zero, indicating that $^{13}NH_3$ had either entered an enormous pool or was metabolically trapped in tissue. Head scintigraphs showed that NH_3 entered brain in proportion to arterial concentration and was more concentrated in gray matter. Based on simple assumptions it was estimated that brain extracts about 50% of arterial blood ammonia. Quantitative body scans showed that brain contained 7.4 ± 0.3% of total observed ^{13}N activity, skeletal muscle 50% and liver 3-24%, depending on its projected area. Uptake and metabolism of NH_3 normally occur in brain, liver and muscle and increase in brain during hyperammonemia. Both muscle wasting due to cachexia and diversion of NH_3-containing blood around liver after portacaval shunting increase the demands on brain for ammonia detoxification.

The Neurochemical Changes in Ammonia Intoxication[66] were referred to by Thomas E. Duffy, M.D., New York Hospital-Cornell Medical Center, New York, NY. Hyperammonemia is associated with chronic hepatic encephalopathy in man, yet acute ammonia intoxication in animals fails to reproduce the clinical and neuropathological changes. Rats were prepared with end-to-side portacaval (PC) shunts to induce chronic hyperammonemia. At eight weeks postsurgery, sham-operated and PC rats received 5 mmol./kg. of ammonium acetate to mimic the situation in patients with liver disease who suffer from superimposed ammonia intoxication. In PC rats, NH_3 loading caused lethargy within 10 minutes and by 30 minutes coma lasting 2-5 hours; control rats became only mildly obtunded and recovered after 30 minutes. The EEG in NH_3-treated PC rats showed bilateral slowing and triphasic waves. In paralyzed, lightly anesthetized animals, NH_3 loading caused disturbances of cerebral carbohydrate, amino acid and energy metabolism that correlated in time with the changes in functional state. During precoma (10 min.), most glycolytic intermediates were increased, as was the lactate/pyruvate ratio. Citrate declined, despite a two-fold rise in pyruvate, suggesting that conversion of pyruvate to citrate had been impaired. The putative neurotransmitters, glutamate and aspartate, declined during precoma but cerebral energy balance remained normal. During coma (60 min.), ATP declined in all regions of brain. The results indicate that cerebral dysfunction in chronic, relapsing ammonia intoxication is not due to primary energy failure. Rather, it appears that NH_3-induced depletion of glutamic and aspartic acids and inhibition of cytoplasmic-mitochondrial hydrogen transport are the dominant neurochemical lesions.

Julien F. Biebuyck, M.D., University of Capetown, Union of South Africa, augmented these presentations with Correlation of Plasma and Brain Amino Acid and Putative Neuro-Transmitter Alterations during Hepatic Coma.[67-71] Neurochemical alterations in hepatic coma were studied by a rapid brain sampling and freezing technic in an animal model produced in Long-Evans male rats by portacaval shunt, followed by hepatic artery ligation. Physiologic parameters such as temperature and blood gas status, which might influence the results, were carefully controlled. The study correlated changes in brain amino acids and other putative neurotransmitter substances with several relevant variables including plasma levels of amino acids, glucose and insulin. Plasma free tryptophan and brain tryptophan were markedly elevated during hepatic coma despite raised plasma levels of the branched-chain amino acids (valine, leucine and isoleucine), methionine, tyrosine and phenylalanine and raised plasma insulin. These changes were accompanied by raised brain ammonia, glutamine, tyrosine and phenylalanine and lowered brain levels of glutamate. Brain cyclic AMP and GABA levels were unaltered. The plasma-free tryptophan and branched-chain amino acid levels were found to increase only after hepatic artery ligation, whereas plasma methionine, tyrosine and phenylalanine were already increased following portacaval shunt only. When intravenous infusion of a specific amino acid mixture (F080, McGraw) was begun at the time of portacaval shunt, brain glutamine levels following hepatic artery ligation remained within the normal range (mean 7.1 μmol/g.w.w.). In contrast the elevated levels (mean 17.3 μmol./g.w.w.) developed in the absence of intravenous amino acid infusion. Other neurochemical changes were, however, unaltered. The pattern of plasma branched-chain amino acids before and after hepatic artery ligation paralleled the differences reported earlier between patients with chronic versus acute hepatic encephalopathy.

Then Josef E. Fischer, M.D., Massachusetts General Hospital, Boston, MA. reviewed the Current Status of the False Neurotransmitter Hypothesis.[72-76] The initial hypothesis of a role for false or substitute neurochemical transmitters in hepatic encephalopathy envisioned a replacement of adrenergic neurotransmitters in phylogenetically primitive portions of the brain dealing with posture, wakefulness and other vegetative processes by inactive or possibly inhibitory neurochemical transmitters such as octopamine and phenylethanolamine. An excellent correlation between grades of encephalopathy and plasma levels of octopamine in both man and animals has been confirmed by several laboratories. The implication, however, of these substances in hepatic coma has been only indirect. Moreover, these substances are locally synthesized in the brain and do not cross the blood brain barrier. Their synthesis is controlled by various factors but principally the concentration of free (unbound) tryptophan within plasma. Brain serotonin, a known inhibitory neurotransmitter which may be taken up by the adrenergic system, has been found to be markedly increased in absolute amounts as well as synthesis and turnover during hepatic coma. Serotonin is increased, however, in mid line structures such as the median raphe but not necessarily within other, nonmid line, structures. Thus, measurements of neurotransmitter levels in whole brain are of little value in view of these wide regional differences.

Recently, serial measurements of the CSF metabolites of various neurotransmitters in experimental hepatic coma have shown that as encephalopathy develops, phenylethanolamine, octopamine, and 5-hydroxyindoleacetic acid (HIAA) rise precipitously. With treatment using an amino acid solution rich in branched-chain amino acids and deficient in aromatic amino acids, awakening of the animal is associated with a precipitous fall in octopamine, phenylethanolamine and HIAA. These experiments provide direct evidence of normalization of cerebral neurotransmitter metabolism in parallel with improvement in hepatic encephalopathy, and reversal of the abnormal pattern seen in early encephalopathy by specific therapeutic intervention.

In the subsequent discussion, Leslie Zieve, M.D. reported that instillation of octopamine into the lateral ventricles of rats in quantities sufficient to increase brain octopamine 20,000 fold and reduce brain norepinephrine and dopamine by 66% and 47%, respectively did not produce coma. This negated a primary role in neurotransmitter abnormalities in induction of coma during hepatic failure. It was pointed out in subsequent discussion that the changes in neurotransmitter levels in specific, possibly critical, brain location were not established by these studies, which involved measurements only in whole brain.

CEREBRAL EDEMA IN FHF

In a session moderated by Fred Plum, M.D., New York Hospital-Cornell Medical Center, New York, NY, Mechanisms of Cerebral Edema Formation[77-81] were discussed by Robert A. Fishman, M.D., University of California, School of Medicine, San Francisco, CA. Brain edema has been classified as vasogenic, cytotoxic or interstitial (hydrocephalic) based on the extent of endothelial cell permeability, the composition of the edema fluid and whether the extracellular fluid space is increased or decreased. Cytotoxic edema is characterized by cellular swelling (neuronal, glial and endothelial) with a reduced extracellular fluid space. Intracellular sodium is elevated and intracellular potassium falls in association with a fall in phosphocreatine, ATP and energy charge potential. CSF protein is usually normal. Cytotoxic edema occurs with hypoxia, acute hypo-osmolality, exposure to certain toxins (e.g. tri-ethyl tin) and with granulocytic brain edema in purulent meningitis and brain abscess.

Brain edema contributes little to the encephalopathy of chronic hepatic disease. In contrast, brain swelling, often with herniation, is increasingly being reported in FHF. While the pathologic features of chronic hepatic encephalopathy are well established (e.g. Alzheimer Type II astrocytosis, etc.), the brain edema of FHF has received little attention. Cytotoxic brain edema is a major and often fatal complication of Reye's syndrome, the encephalopathy of which is associated with intracranial hypertension. This classification of the edema in Reye's syndrome is supported by a normal CSF protein content and by electron microscopic findings of astrocytic swelling and intralamellar blebs in the myelin. These findings have not been described in other forms of FHF. Both the metabolic basis of the brain edema of FHF and its neuropathology require further study in clinical material and in experimental models. Definition of the mechanism of brain swelling has important implications for therapy. Cytotoxic edemas, for example, tend to respond poorly to corticosteroid therapy, which is now commonly employed as empirical treatment for suspected cerebral edema in FHF.

Athol J. Ware, M.D., University of Texas, Southwest Medical Center, Dallas, TX, spoke about Incidence of Cerebral Edema in FHF.[82-85] That cerebral edema is a rather frequent complication of FHF has only been recognized in recent years. In a major review in 1951, Walshe specifically commented on the normal macroscopic appearance of the brain at autopsy after massive hepatic necrosis. Lucké mentions, only in passing, the occurrence of cerebral edema in fulminant viral hepatitis. In 1969, however, Pirola pointed out the potential significance of this entity as an immediate cause of death in FHF. A review of 53 patients with FHF seen in Dallas from 1958-1970 identified 32 patients studied at autopsy. Sixteen had cerebral edema and four of these had cerebellar and/or uncal herniation. The factors associated with this finding were: 1. young age, 2. absence of terminal azotemia or acidosis and 3. a prolonged period of stage IV coma. Cerebral edema was not correlated with any therapeutic modality. A more recent review of Gazzard, et al demonstrated cerebral edema in 36 of 92 (38%) FHF patients coming to autopsy. Twelve had cerebellar tonsillar herniation and eight had herniation of the temporal lobes. These authors confirmed the association with a younger age but did not find a correlation with duration of stage IV coma, acidosis or azotemia. Cerebral edema is thus a frequent complication in FHF from a variety of causes. It may precipitate death, its antemortem diagnosis is difficult and its management, at present, is probably ineffectual.

This presentation provoked considerable discussion of the criteria for postmortem diagnosis of cerebral edema. Brain weight, macroscopic ventribular dilatation and histologic features are commonly used but several speakers considered histologic examination often unreliable.

Roger Williams, M.D., Liver Unit, Kings College Hospital, London, England, spoke about Cerebral Edema in an Experimental Model of Fulminant Hepatic Failure: Effect of Corticosteroids. In a survey of 105 patients dying from FHF, cerebral edema was found in 38%. In half, death could be attributed to it. No consistent benefit was observed from dexamethasone. Intracranial pressure (ICP) was studied in a surgically induced model of FHF. Following induction of hepatic infarction in the pig, serial EEG recordings showed progressive slowing of the frequency with decreasing amplitude, and blood ammonia rose. Monitoring of ICP by subdural pressure transducer demonstrated a progressive and reproducible rise from 12.81 ± 2.52 (SE) mm. Hg. immediately after the operation to a mean value of 51.60 ± 11.86 mm. Hg. just prior to death eight to 16 hours later. Autopsy showed marked cerebral edema with flattening of the gyri. In controls, ICP rose slightly but returned towards normal (8.0 ± 2.5 mm. Hg.) eight hours after laparotomy. There was a statistically significant difference between ICP levels of test animals and controls ($P < 0.001$). Methylprednisolone (100 mg./kg. initially followed by 25 mg./kg. 2 hourly) at the start of surgery completely abolished the rise in ICP. In contrast, no effect was seen if the drug was given four hours after surgery. The early and progressive rise in ICP was unexpected. If corticosteroids are to be effective in preventing this complication they must be given as early as possible after the onset of FHF.

Changes in the Blood-Brain Barrier in the Hepatic Coma Following Hepatectomy were described by Carl A. Goresky, M.D., Montreal General Hospital, Montreal, Canada. Pathogenesis of the coma following massive hepatic necrosis or hepatectomy has never been defined. The possibility that an abnormality at the blood-brain barrier may play a role was investigated. Bloodless two-stage hepatectomies were performed on Wistar rats maintained by intravenous glucose infusions. In late stage III or IV hepatic coma the functional integrity of the blood-brain barrier was assessed by: 1. the sudden arterial injection/15 second decapitation Oldendorf tissue residue technic and 2. by intravenous Trypan blue. The former showed that the barrier had become permeable to D-glucose, insulin and L-glucose, which do not cross the normal barrier and the latter that the barrier had also become permeable to Trypan blue. The brains of comatose animals showed cerebral edema grossly, their water contents being increased and swollen astrocytes, especially in pericapillary locations on electron microscopy. Thus, the break in the blood-brain barrier promotes cerebral edema, permitting some substances to gain abnormal access to the brain parenchyma, as well as the escape of substances usually conserved, such as neurotransmitters.

The session ended with a spirited discussion under the leadership of Dr. Plum. Participating neurologists indicated that they had generally been skeptical that the cerebral edema of FHF was anything other than a terminal, hypoxic event. There was now a consensus that the situation was more complex and represented a hitherto unrecognized neurological complication of liver disease requiring intense collaborative studies among neurologists and hepatologists with primary interest in hepatic failure.

DYSFUNCTION OF OTHER ORGANS IN FHF

The sessions on cerebral aspects of the syndrome were followed by one moderated by Telfer Reynolds, M.D., University of Southern California, Los Angeles, CA, Peter N. Trewby, M.D., Liver Unit, King's College Hospital, London, England, reported on The Consequences and Hemodynamic Mechanisms of Hypotension in FHF.[86, 87] Hypotension was an important complication in 82 of 94 patients studied in grade IV coma due to FHF. Sixty per cent of the time spent hypotensive could not be explained by hemorrhage, septicemia and electrolyte or blood gas changes. Hemodynamic measurements during such episodes showed that inappropriate systemic vasodilatation rather than primary heart failure was often the cause of the low blood pressure. Similar pulmonary vasodilatation was suggested by significant increase in pulmonary venous admixture. Morphometric studies at autopsy showed abnormal dilatation of the pulmonary arterioles, the pulmonary capillaries and also the pleural vessels, providing an anatomical basis for the physiological changes during life. When arterial hypotension was induced in an animal model of FHF there was a striking reduction in both cerebral blood flow and cerebral metabolic rate for oxygen. The reduction became even more marked as the animals developed a raised intracranial pressure due to cerebral edema. In man the use of adequate fluid replacement, if necessary with an inotropic agent, may reduce the incidence of hypotension and so prevent this important secondary cause of brain damage.

Renal Dysfunction in FHF[88-90] was discussed by Laurence M. Blendis, M.D., Toronto General Hospital, Toronto, Canada. In a retrospective study of 48 patients with FHF in grade III or IV coma, 38 showed renal impairment. This represented prerenal uremia in four and either acute tubular necrosis or "functional renal failure" in the rest. The frequency and type of renal impairment were not related to the etiology of the FHF. Abnormalities in plasma electrolytes were common, especially hypernatremia, which often followed infusion of large amounts of fresh frozen plasma either in the absence of a naturesis or with the use of osmotic diuretics. These electrolyte abnormalities led to a modification of therapy in subsequent patients. In a prospective study, renal function was evaluated in 40 patients with FHF divided into two groups on the basis of glomerular filtration rates, which were either greater than 40 ml./min. or less than 25 ml./min. A number of patients in the former group had markedly abnormal renal retention of sodium together with a reduced free water clearance and low potassium excretion, which could be explained by increased proximal tubular reabsorption of sodium. The patients in the second group had evidence that renal tubular integrity was maintained even with glomerular filtration rates as low as 3 ml./min., (i.e. functional renal failure). In 28 patients with FHF, alkalemia was common. This was associated mainly with a low P_aCO_2 but a raised plasma bicarbonate was found in 16 instances. Metabolic acidosis was present in only four patients, of whom two had taken paracetamol overdose. In two, this disturbance represented lactic acidosis.

Peter T. Flute, M.D., St. George's Hospital, London, England, then discussed Blood Coagulation Defects in FHF[91-96] in considerable detail. Multiple abnormalities of the coagulation and fibrinolytic systems in fulminant hepatic failure mean that hemostatic potential is always impaired but bleeding is not inevitable unless hemostasis is challenged by damage to blood vessels. The abnormalities can be classified as resulting from quantitative defects in synthesis, increased catabolism, or qualitative defects in synthesis.

Defective hepatic synthesis may affect coagulation or fibrinolytic factors (enzyme precursors) or the inhibitors of the active enzymes. The former is the predominating change, the over all effects being easily monitored by the one-stage prothrombin time or by the thrombotest method. Factor VII levels fall first (shortest half-life) and are little affected by increased catabolism. Factor V falls are a useful indication that hepatic damage has occurred independently of the Vitamin K dependent factors II, VII, IX, and X. Fibrinogen (factor I) falls last and the liver preserves a capacity for increased synthesis of this factor until the last stages of failure. Factor VIII levels initially rise, perhaps due to a reactive increase in synthesis of Factor VIII-related protein by vascular endothelium. In the final states, factor VIII levels fall probably due to increased catabolism.

Increased catabolism has been measured directly for fibrinogen, platelets, prothrombin and plasminogen. In health, the fractional catabolic rate of fibrinogen is independent of the total fibrinogen plasma pool. In hepatic failure the fractional catabolic rate is increased suggesting the addition of an unusual route of metabolism. Since the increase is returned towards normal by heparin administration and is associated with small but significant increases of soluble fibrin monomer complexes and fibrin degradation products, this suggests an element of intravascular coagulation.

Qualitative defects in synthesis of fibrinogen have recently been confirmed. In FHF the long thrombin and reptilase times are related to delay in the polymerization phase of fibrin monomer similar to that reported in some of the congenital dysfibrinogenemias.

Quantitative defects in synthesis may require replacement with fresh blood, fresh frozen plasma or coagulation factor concentrates, in addition to parenteral Vitamin K. Transfusion usually fails to correct the prothrombin time, due to the short half-life of some factors and to the pathological increase in catabolism. Qualitative dysfibrinogenemia can probably be ignored, since many congenital disorders of this type show no sign of bleeding. The principle, however, that abnormal proteins with defective function can be synthesized may be of fundamental significance to the understanding of the condition. Increased catabolism with its element of intravascular coagulation is usually not severe, little if at all greater than that found after surgical operations or in normal pregnancy. It shows a predisposition to intravascular fibrin deposition, however, which may cause organ damage if stimuli are accentuated as by infection or the transfusion of active coagulation factors in certain concentrates, or if normal compensation is impaired, by the administration of inhibitors of fibrinolysis.

Heinrich Liehr, M.D., University of Würtzburg, West Germany, next discussed the Significance of Endotoxemia in FHF and its Clinical and Experimental Implications.[97-101] Endotoxemia occurs frequently (63-100%) in FHF. It is thought to contribute significantly to the liver injury and is believed to result from intestinal endotoxin absorption, portal endotoxemia and insufficient clearance of endotoxins by the hepatic reticuloendothelial system (RES). The importance of the RES and endotoxemia can be demonstrated by an experimental model, galactosamine (GalN) hepatitis in the rat. The liver injury in this model can be prevented by RES stimulation, or made fatal, with FHF, by RES blockage. Prior colectomy prevents the development of both GalN induced hepatitis and liver cell necrosis, although the biochemical response to GalN is still present, whereas administration of GalN together with sublethal doses of endotoxin leads to FHF. The complement system, activated by endotoxins via the C_3-pathway, was found to be the ultimate mechanism of action leading to complement mediated cytolysis of hepatocytes and hepatitis. This is supported by the results obtained by using genetically CH_{50}-depleted mice. These mice are refractory to the development of liver cell necrosis and hepatitis after GalN administration, although they develop endotoxemia. Whether the hepatocyte membrane defect induced by galactosamine is also of significance as a precondition of liver cell necrosis has not yet been established.

The GalN experimental model has some parallelisms with severe hepatic injury in man, such as the presence of endotoxemia, complement activation and viral-induced membrane defects. Certain extrahepatic manifestations of FHF such as renal failure and consumption coagulopathy appear due to endotoxin action, both in the GalN model and in man.

Both experimental and clinical data suggest that endotoxins are of pathogenetic significance in FHF and that FHF is the consequence of endotoxin action, and not vice versa.

ETIOLOGY OF FHF

The conference next turned its attention to this topic under the chairpersonship of Sheila Sherlock, M.D., Royal Free Hospital, London, England.

James W. Mosley, M.D., University of Southern California, Los Angeles, CA described the role of Viruses in the Etiology of Fulminant Hepatic Failure. Type A hepatitis and type B hepatitis can now be specifically diagnosed; if the test results indicate neither, then non-A, non-B hepatitis is the presumptive etiology. The patient with fulminant viral hepatitis who does not survive, however, presents special problems. Hepatitis A virus (HAV) is likely to be undetectable in fulminant cases unless the complication supervenes very early. HAV can be presumptively diagnosed, however, if the patient has antibody detectable by immune electron microscopy (IEM) but not by immune adherence hemagglutination (IAHA). If the patient survives, the appearance of IAHA antibody in convalescence is diagnostic. For type B hepatitis, the presence of HB_sAg in the acute phase is strongly presumptive of a hepatitis B virus (HBV) etiology, and its disappearance in survivors is diagnostic. HB_sAg negativity, however, does not rule out type B hepatitis; the finding of anti-HB_c positivity and anti-HB_s negativity would also be diagnostic, as would the appearance of anti-HB_s in convalescence when there is survival. If none of these patterns is observed, then non-A, non-B disease is diagnosed presumptively.

Rakela and co-workers in Los Angeles reviewed 125 cases of fulminant viral hepatitis from 1969 to the present, and found that 60% had been HB_sAg-positive when tested on admission. The Coordinating Center for the Acute Hepatic Failure Study Group (AHFSG) evaluated sera from 49 patients seen in 1975 and 1976 in all parts of the United States. Only 15 of these cases (31%) were confirmed as HB_sAg-positive. The differences in frequency of easily identified type B disease is undoubtedly due in part to the character of the patient populations served. Anti-HB_c assays have not been completed, so that no definite statement can be made concerning relative proportions of HB_sAg-negative cases of fulminant type B disease. Forty-two of the HB_sAg-negative patients of Rakela, et al for whom sera were still available and all 34 of the AHFSG's patients were studied using the newly developed indices of HAV infection, resulting in detection of seven cases among the former and two among the latter. Reliability of the pattern of IEM positivity-IAHA negativity in the acute phase was supported by IAHA conversion in the three patients who survived.

One patient in the Los Angeles series and three in the AHFSG series exhibited both HB_sAg *and* an IEM-IAHA pattern compatible with type A hepatitis. Infection by HAV and HBV have been reported to have occurred either simultaneously or in close proximity and the results indicated are compatible with the possibility. It is also plausible that such dual infections could more frequently lead to severe disease including FHF.

Common Nonviral Causes were then discussed by Jean-Pierre Benhamou, M.D., Hôpital Beaujon, Clichy, France. Of 275 French cases of FHF recently reviewed, 85% were attributed to viral hepatitis and only 15% (40 cases) to nonviral causes. The most common nonviral cause was toxic hepatitis (25 cases) due to such agents as white phosphorous, hydrocarbons and mushroom poisoning with *Amanita phallalloides* and related fungi. White phosphorus ingestion, usually the result of suicide attempts, responds to early exchange transfusion if administered before severe hepatitis develops. Hydrocarbon toxicity, often the result of industrial exposure, is associated with characteristic early confusion which may be a clue to diagnosis. Mushroom poisoning presents with a severe diarrheal prodrome and occurs in France most often among characteristic immigrant groups. Drug reactions (eight cases) were the second most common nonviral etiology, with INH a common offender. There is a suggestion that the simultaneous administration of rifampicin accelerates the development of INH hepatotoxicity. Ischemic necrosis (four cases) and acute Wilson's disease (three cases) constituted the remainder of the series. The ischemic necrosis was secondary to Budd-Chiari syndrome in three instances and heart failure in one. Acute Wilson's disease is characterized by very high serum and urine copper, acute intravascular hemolysis, and the development of hepatic failure with encephalopathy after two to six days. It has proved invariably fatal despite intensive copper chelation therapy. Since the use of drugs for suicide attempts, the consumption of wild mushrooms and industrial hygiene procedures vary from country to country, the proportion of cases of FHF due to nonviral causes may also be expected to vary considerably.

Assessment and Prognosis in FHF

The seventh session was under the chairmanship of Fenton Schaffner, M.D., Mount Sinai School of Medicine of the City University of New York. Sheila Sherlock, M.D., Royal Free Hospital, London, England, discussed General Clinical and Biochemical Assessment of the Patient.[102-107] This report is based on 140 patients with FHF in grade III or more coma seen at the Royal Free Hospital between 1969 and 1976. A distinction has to be made between the prediction of which patient with acute hepatocellular disease will proceed to FHF and the assessment of the patient who is transferred to a special unit already in FHF. In predicting a fulminant course, age, sex (males at greater risk), obesity, immunological status, etiology, clinical course, state of consciousness, rate of development of jaundice and liver size are important. Predictive biochemical changes include drug levels (e.g. acetaminophen) and serial measurements of bilirubin, albumin, prothrombin and C_3 but not alphafetoprotein or transaminases. In particular, progressively falling levels of albumin, prothrombin and C_3 suggest severe hepatic damage with impending failure. HB_sAg should be measured but neither it nor other HB_sAg-associated markers such as "e" seem related to development of a fulminant course.

In established FHF with coma, a distinction must be made between acute hepatic failure and acute superimposed on chronic liver disease. A long history, a very large, hard liver with a palpable spleen, spider nevi and poor nutrition clearly indicate the latter. Acute alcoholic hepatitis is placed somewhere between acute and acute on chronic. It should be treated as FHF. In view of the reports of acute Wilson's disease with FHF, eyes must be screened for Kayer-Fleischer rings.

Proper management of cases in deep coma require serial measurements of consciousness, liver size, blood pressure, blood glucose, serum electrolytes and creatinine, blood gases, blood clotting and urine output to promptly detect and deal with changes.

The Neurologic Assessment of Hepatic Coma[108, 109] was then described by Fred Plum, M.D., New York Hospital-Cornell Medical Center, New York, NY. Both accurate diagnosis and assessment of treatment in hepatic encephalopathy require at least a semiquantitative appraisal of clinical neurological status and how it changes from day to day. Neurologically, early hepatic encephalopathy produces varying degrees of bilateral forebrain dysfunction but relatively little direct impairment of brain stem function until the terminal stages of the disease. A persistent problem is that once confusion or stupor appear, many authors tend simply to classify the condition as hepatic coma, overlooking that the category includes wide differences in neurological function with correspondingly different potentials for recovery. As part of an international cooperative study between the Royal Victoria Hospital, Newcastle on Tyne, UK and the New York Hospital-Cornell Medical Center for evaluating the outcome of patients with medical coma, a clinical coma profile or scale (Table I) for bedside use was developed that separately appraises the state of six distinct forebrain and brain stem functions. The profile meets the requirements of simplicity, of showing only small interobserver inconsistencies and of giving a numerical score. It has been applied effectively in a prospective study of prognosis in over 300 cases of medical coma including 33 patients with hepatic encephalopathy. Results indicate a high correlation between best-worst initial coma scores and similar outcomes; they also indicate that day to day changes in the score correlate well with improving or worsening outcomes. To date, the presence or absence of oculovestibular reflexes is the best single predictor of outcome in patients with medical coma.

TABLE I

A CLINICAL COMA-PROFILE FOR BEDSIDE USE*

- I. *Verbal response*
  - None
  - Incomprehensible
  - Confused
  - Normal
- II. *Eye opening*
  - None
  - Noxious stimuli only
  - Verbal stimuli
  - Spontaneous
- III. *Pupils*
  - Nonreactive
  - Sluggish
  - Brisk
- IV. *Oculocephalic-oculovestibular*
  - No reaction
  - Partial or dysconjugate
  - Full
  - Normal
- V. *Best motor response*
  - None
  - Abnormal extensor
  - Abnormal flexor
  - Withdrawal or localizes
  - Obeys commands
- IV. *Respiration*
  - Nil on ventilator
  - Irregular
  - Regular > 22/min.
  - Regular > 22/min.

* Participants for the Coma Study include from the U.K.: D. Bates, N. E. F. Cartlidge, R. Knill-Jones, R. J. Leigh and D. Shaw; from the U.S.: J. E. Caronna, J. Dougherty, D. E. Levy, F. Plum and R. Van Uitert.

As a follow-up to the preceding paper, Bruce MacGillivray, M.D., Royal Free Hospital, London, discussed The Electroencephalogram in Acute Liver Failure.[110-113] The EEG pattern changes in a predictable way in acute hepatic failure, in parallel with the clinical state. The changes are quantifiable by methods based on the frequency content and amplitude of the trace recorded under standard conditions. Using these technics, it is possible to derive simple parameter synoptic curves which apply across most subjects and are useful in monitoring the clinical state. The triphasic wave is not specific to hepatic coma, occurs in about 10% of subjects but not in patients under 20 years of age. This suggests that it is a phenomenon related to cerebral maturity. Although arguments have been advanced in favor of a variety of causal agents, no consistent correlation between any single factor and the observed EEG changes has been demonstrated. Detailed analysis of the EEG in liver disease offers some clues as to the likely mechanisms underlying the observed alterations but present knowledge of the nature of EEG generation is insufficient for these notions to be other than speculative. Some support is advanced for the hypothesis that there is a constitutional (genetic) component in the EEG changes, recognition of which may help to clarify some currently confusing observations.

Liver Biopsy and Prognosis[85, 114, 115] was then discussed by Pierre Opolon, M.D., Hôpital Saint Antôine, Paris, France. In 1973, results were reported from percutaneous liver biopsy in 38 patients with FHF and coma, including serial biopsies in 22. With appropriate preconditions, the procedure was performed safely. Stereological estimation of hepatocyte volume fraction (HVF) was correlated with levels of clotting factors. Early liver biopsy allowed estimation of prognosis in 55% of the cases. All patients with HVF of $< 35\%$ and thromboplastin time $\leqq 10\%$ died; all patients but two with HVF $\geqq 35\%$ and thromboplastin time $> 10\%$ recovered consciousness ($n = 9$) or at least showed evidence of marked liver regeneration ($n = 2$). On serial liver biopsy, a significant increase in hepatocyte volume and clotting factors was observed only in patients who ultimately recovered consciousness. The estimated liver cell mass after regeneration in patients who recovered consciousness was invariably $\geqq 45\%$ and $< 45\%$ in the patients who did not. Two further series have confirmed these observations. More recently, in a retrospective study of 21 fatal cases with both serial liver biopsies and autopsy examination, HVF did not increase during course of the illness (early liver biopsy $= 23\% \pm 17\%$, postmortem liver biopsy $= 24\% \pm 17\%$). Hence, estimation of HVF on liver biopsy during FHF allows good estimation of liver cell mass and ultimate prognosis in approximately 50% of cases. Moreover, serial liver biopsy may be particularly useful to assess liver regeneration.

Joseph R. Bloomer, M.D., Yale University, School of Medicine, New Haven, CT, reported on the Prognostic Value of Alpha-Fetoprotein in FHF.[116-120] By radioimmunoassay, serum levels of α-fetoprotein (AFP) are frequently elevated in nonneoplastic hepatic diseases in which there is prominent necrosis and inflammation of the liver parenchyma. Evidence suggests that this reflects hepatic regeneration, rather than being directly related to necrosis *per se*. Serum AFP was measured serially in 12 patients with massive hepatic necrosis in order to determine the onset of increased serum AFP, since this may provide information concerning the course of regeneration. Ten patients had viral hepatitis, one halothane hepatitis and one massive ischemic necrosis. Eleven of the patients died. The duration of illness was dated from the onset of the first symptoms attributable to liver disease. Increased serum AFP (> 40 ng./ml.) was not observed in any patient before the ninth day of illness. Levels rose significantly, however, in eight of the nine patients who died between the 10th and 60th day and in the one patient who survived. All nine patients with increased levels of serum AFP exhibited histological evidence of hepatic regeneration. These findings indicate that the rise in serum AFP following massive hepatic necrosis is related to the duration of survival after the onset of illness but does not necessarily imply ultimate recovery. If serum AFP accurately reflects the time course of hepatic regeneration, it would appear that regeneration in FHF is delayed until the second week of illness.

Another paper in this session was presented on the Galactose Elimination Capacity as a Prognostic Index in FHF by Niels Tygstrup, M.D., University Hospital, Copenhagen, Denmark. Most so-called liver function tests do not truly reflect the functional capacity of the liver. Tests which accurately determined functional capacity or "functional hepatic mass" might be of particular value in assessing both initial prognosis and response to therapy in FHF. Therefore, in 25 patients with FHF the prognostic value of a qualitative liver function test, the galactose elimination capacity (GEC), as assessed and compared with routine liver tests and clinical features.

GEC was significantly higher ($P < 0.05$) in the five patients who survived than in the 20 patients who died. None of the other routine liver tests was significantly different between survivors and nonsurvivors. Patients with GEC below 12.8 μmol./min./kg. invariably died. Among patients who died despite GEC greater than 13 μmol., most had a subacute course of the disease. Quantitative liver tests, such as the GEC may be useful in estimation of prognosis and/or therapeutic response. Such procedures may identify cases with a high chance for spontaneous survival, thus avoiding dangerous experimental therapies.

Hepatic Regeneration: Normal Regulation, Abnormalities in FHF: Possible Therapeutic Implications[121-125]

A special lecture was delivered by Nancy Bücher, M.D., Massachusetts General Hospital, Boston, MA. Partial hepatectomy in the rat induced a rapid burst of proliferative activity. Hepatic regeneration was greatly delayed and diminished in partially hepatectomized rats, surgically deprived of portal splanchnic viscera and a portal blood supply; it was restored to the normal rate by continuous infusion of insulin and glucagon but not by either hormone alone. Similarly, continuous infusion of these two hormones into mice with 100% lethal viral hepatitis (A-59 murine hepatitis virus) doubled mean survival time and led to recovery in 40%; insulin alone had much less effect and glucagon none. Hence, in two animal models involving extensive liver loss or necrosis, insulin and glucagon acted synergistically to enhance hepatic growth and function.

In normal rats partial hepatectomy was followed by an abrupt fall in portal vein insulin and a sharp rise in glucagon content, consistent with a relatively low dose of insulin and a high dose of glucagon empirically determined to be optimal in the above rat and mouse models. Although the pancreatic hormones greatly potentiate, they do not initiate hepatocyte proliferation. In the case of mouse hepatitis the hormones also are protective. The means by which these effects are implemented are being sought; possible roles of cyclic nucleotides and newly discovered phosphorylated nucleotides are currently under study.

Many hepatic growth-regulatory factors have been proposed. Growth regulation may reside in particular combinations of such factors specific for each cell type. A promising approach to FHF may be to discover and apply knowledge of these factors both to provide possible protection from continuing injury and to promote repair and regeneration.

Causes of Death in FHF[85]

A detailed review was presented by Bernard Rueff, M.D., Hôpital Beaujon, Clichy, France. The study was based on 210 cases which had been treated only with glucose, antibiotics and ventilatory assist.

As in the earlier British review, the largest single cause of death was neurologic complications, which accounted for 67% in the French series (half with cerebral edema), and only 35% in the British. In both series, the incidence of cerebral edema was higher among younger patients. Bacterial infection (13%), massive gastrointestinal hemorrhage (12%) and hemodynamic deaths (8%, half with cardiac failure) were the other major causes of demise in the French series. As in the earlier report, thrombocytopenia was a major factor associated with a high risk of bleeding. Pancreatitis was found in several instances, even in the absence of steroid therapy. Approximately two-thirds of the cases developed elevated α-fetoprotein levels but only 10% had histologic evidence of regeneration.

Identification of the causes of death may be crucial in improving survival if specific therapy for the complications identified is available. The data suggest that a major effort is required to understand the mechanisms and to evolve effective treatment for the edema of FHF. This complication does not appear to result solely from the use of experimental therapies, such as charcoal perfusion.

TREATMENT OF FHF

This session was directed by Allan G. Redeker, M.D., University of Southern California, Los Angeles, CA. The first speaker, James W. Mosley, M.D., University of Southern California, Los Angeles, CA, discussed Effects of Improved Intensive Care on Survival.[126] Although massive hepatic necrosis was a recognized complication of viral hepatitis 60-90 years ago, the encephalopathy of FHF was sufficiently well recognized only in the 1940's to permit antemortem diagnosis and assessment of survival. The literature, however, is a poor guide to changes in prognosis, because of the tendency to report single or small groups of cases when they happen to be nonfatal. Even larger series are not necessarily representative. Nevertheless, survival from FHF in the 1940's and 1950's was apparently no more than 10%. In contrast, two recent cooperative series from the United States indicated over all survival of 26%. Even with patients present in stages III or IV coma, survival is now 21%. These estimates suggest that there has been a small improvement in survival over the last two to three decades. None of the therapies during that time seems likely to have been responsible for any improvement in outlook. The monitoring of vital functions and immediate intervention in cardiac, respiratory and other emergencies, however, has developed rapidly in the last 15 years. The need for such services in acute hepatic failure is easily illustrated. In a recent study, 39% of patients experienced cardiac arrhythmia or arrest, 41% had respiratory distress or arrest and 32% had gross gastrointestinal bleeding, all of which can now be handled effectively in the setting of an intensive care unit. The apparently improved survival in some studies involving new methods of treatment may be due more to the proximity of an unusual number of physicians and nurses concerned with the success of the new procedure and to expert intensive care than to the procedure itself. This is one of the reasons why randomized rather than historical controls are so essential to the assessment of such procedures. Indeed, it is plausible that the over all fatality rate could probably be improved further if all patients with acute hepatic necrosis were managed in regular intensive care units instead of the isolation rooms which prevent some patients from receiving the close observation they require.

Arnold L. Smith, M.D., Childrens Hospital, Boston, MA, followed with a presentation on the Management of Cerebral Edema in Reye's Syndrome: Its Contribution to Ultimate Outcome.[127-131] Virus-induced, acute mitochondrial damage in virtually every organ system appears to be the basic lesion in Reye's syndrome. The biochemical changes in the serum are dramatic but the mitochondrial enzymatic deficits are transient. Milder illness is associated with complete recovery regardless of the type of therapy. Death, when it occurs, is almost always due to cerebral edema. A staging system based on neurological and encephalographic criteria allows more exact definition of severity of disease. Intensive anticerebral edema therapy administered according to the severity of brainstem signs (a sluggish pupillary reaction, slow occulovestibular reflex and absent ciliospinal reflex) to ten patients with Stage IV disease (uniformly fatal with simple supportive care) permitted a 50% survival rate. Intracranial pressure monitoring in four patients by means of a ventricular cannula documented a correlation between increased intracranial pressure and neurologic deterioration. Intravenous mannitol was administered when intracranial pressure exceeded 15 mm. Hg., or when cerebral perfusion was less than 50 mm. Hg. One of four patients experienced cerebral death with low intracranial pressure. Methods reducing intracranial pressure in Stage IV Reye's Syndrome will permit an increased survival. It has yet to be established whether such approaches are relevant to the cerebral problems observed in the conventional FHF.

Nigel Stanley, M.D., Middlesex Hospital, London, England, reviewed Respiratory Aspects of Therapy. Pulmonary complications are common terminal events in FHF and endotracheal intubation should be performed at the onset of coma to prevent aspiration and to facilitate bronchial cleansing. The detrimental effects of cerebral hypoxia should be avoided by oxygen administration. Restoring normal arterial saturation may require high concentrations of inspired oxygen in cases with pulmonary edema, arteriovenous anastomoses and pneumonia, which behave physiologically as right-to-left shunts. Refractory arterial hypoxemia in severe pulmonary edema may respond to mechanical ventilation with positive end-expiratory pressure (PEEP). Oxygen should also be given to improve cerebral oxygen delivery in cases with anemia or shock, who may have brain tissue hypoxia even when the arterial saturation is normal: No attempt should be made to correct the usual hypocapnia in FHF and assisted ventilation may be helpful in the 5-10% of cases with a respiratory acidosis. The acid-base state should always be checked in patients who have received respiratory depressant drugs, such as sedatives and in those with co-existing chronic lung disease. The benefits, however, of improving the blood gases by mechanical ventilation, especially when using PEEP, must be weighed against its possible adverse effects on cerebral and hepatic circulation.

Steven Schenker, M.D., Vanderbilt University, Nashville, TN, contributed a paper on Treatment of Delirium Accompanying Hepatic Encephalopathy in Fulminant Liver Failure.[132-135] Delirium may occur at the onset of or with resolution of hepatic coma accompanying FHF. It is often brief and, when not associated with convulsions, may be treated without drugs, by good nursing care alone. Severe and/or prolonged delirium, especially accompanied by convulsions, requires drug therapy. The ideal drug for such patients should have: 1. a rapid titratable effect. 2. a short duration of action, 3. normal binding to plasma proteins, 4. not unduly depress the cerebral "receptors" involved in maintenance of consciousness, and 5. not interfere significantly with vital functions (i.e. respiration, blood pressure). No known drug satisfies all these criteria. Of available drugs, there are no data at all about chlordiazepoxide (Librium®) and paraldehyde. Intravenous diazepam (Valium®) has a rapid, easily titratable effect and an elimination half-life of 20-100 hours (proportional to age) in normal man. With liver disease the half-life for total drug approximately doubles and clearance falls appropriately. These effects may be exaggerated if plasma protein binding of diazepam is decreased in FHF, as it is in cirrhosis. In cirrhotics there is suggestive evidence for increased sensitivity of the brain to diazepam, especially with decreased serum albumin. The elimination of phenobarbital is normal in patients with hepatitis and only slightly prolonged in those with cirrhosis. The half-life of the drug, however, is long (85 hours). It may depress vital centers and brain sensitivity to it in patients with liver disease is unknown. Oxazepam (Serax®) is metabolized and eliminated normally and is bound normally to plasma proteins in patients with liver disease. The drug has a short half-life (six hours) but cerebral sensitivity to it has not been studied. It can only be given orally with peak blood level occurring at about three hours. The pharmacokinetics of another benzodiazepine, Lorazepam, which is inactivated like oxazepam by glucuronidation but is available for intravenous use, are now being investigated. Preliminary data suggest that it has a half-life of about 24 hours which is only a little prolonged with liver disease. With severe chronic liver disease plasma drug binding is depressed but is essentially normal in acute hepatitis. The sensitivity of the brain to this drug in patients with liver disease is unknown. In summary: 1. little is known about the use of sedatives/tranquilizers in patients with acute or chronic liver disease; 2. when sedation is necessary, individual titration of dose to response is essential; 3. if oral therapy is possible, oxazepam presently seems to be the drug of choice and 4. if intravenous therapy is essential, then judicious use of small doses of Valium or perhaps Lorazepam (if further validated and commercially available) would be reasonable.

TABLE II

	Treated		Placebo	
	No.	Survived	No.	Survived
Ware, et al, Dallas (1974)	4	0	11	7
Redeker, et al, Los Angeles (1976)	17	6	16	6
Gregory, et al, Palo Alto (1976)	4	0	3	2
EASL (1976)	23	3	18	2
Total	48	9	48	17

Burton Combes, M.D., University of Texas, Southwestern Medical School, Dallas, TX, next summarized the Current Status of Corticosteroids in the Treatment of FHF.[126, 136-140] The rationale for the use of corticosteroids in FHF rests on the presumption that the anti-inflammatory effect of steroids will limit the amount of parenchymal cell necrosis irrespective of the cause. The first reports of efficacy with these agents appeared in the early 1950's. Further uncontrolled experiences supporting steroid therapy in FHF were published and the use of these drugs in this condition became standard practice in many places.

Only recently have efforts been made to assess the usefulness of steroid therapy in FHF in a randomized controlled and prospective manner. Data from four small studies addressing this question are currently available with the results shown in Table II

These data do not show an advantage of steroid therapy but should not be interpreted as showing a disadvantage from such treatment. Definitive information on the value of corticosteroids in FHF should soon become available from the prospective cooperative study being conducted by the Acute Hepatic Failure Study Group under the auspices of the AASLD.

E. Anthony Jones, M.D., Liver Unit, NIH, Bethesda, MD, followed with a discussion of Possible Adverse Effects of Corticosteroids on Nitrogen Metabolism in FHF.[141-148] Definitive data on the effects of corticosteroids on nitrogen metabolism in patients with FHF are not available. Relevant data in patients with chronic hepatocellular disease, however, suggest that they probably have quantitatively appreciable and potentially adverse effects in FHF. In such patients, prednisolone was associated with a significant increase in the plasma urea concentration, the body urea pool and the synthetic rate of urea. Probable mechanisms for the increased incorporation of nitrogen into urea include increased liberation into the circulation of nitrogenous substances, including ammonia, as a result of corticosteroid-augmented protein catabolism in peripheral tissues and increased liberation of ammonia in the intestine. Further studies of the urea synthetic rate and intestinal ammonia liberation, in other patients, confirmed that an increase in plasma urea concentration results in more substrate for the generation of ammonia in the intestine. In FHF an adverse effect of corticosteroids may arise if an increased load of nitrogenous compounds, including ammonia, from peripheral tissues is inadequately metabolized by the liver and if the prevailing synthetic rate of urea, which could be subnormal, is increased by treatment. The data suggest that the magnitude of such adverse effects could exceed the generation of 116 mg. additional ammonia nitrogen/kg./day.

Peter T. Flute, M.D., St. George's Hospital, London, England, then reviewed the rationale for the Prophylactic Treatment of Coagulopathy. Severe gastrointestinal bleeding occurs in up to half the patients with fulminant hepatic failure. All patients, however, show multiple coagulation factor deficiencies and bleeding is not directly related to the severity of the observed changes. Prophylaxis of bleeding may attempt to improve hemostasis efficiency or attempt to reduce the challenge to hemostasis. The first objective involves the parenteral administration of Vitamin K and the replacement of coagulation factor deficiencies by transfusion. Fresh frozen plasma, which contains all coagulation factors, given in amounts up to 2½ l daily, fails to completely correct the prothrombin time in severe cases and carries problems of fluid and sodium load. Coagulation factor concentrates do not include Factor V, many do not include Factor VII and all carry the risk that activated coagulation factors may increase the already established tendency to intravascular coagulation. Recent unpublished observations from King's College Hospital, London, collected by Dr. Roger Williams, failed to show any prophylactic benefit from fresh frozen plasma transfusion on the incidence of severe gastrointestinal bleeding in patients with grade IV coma. The alternative objective, reduction of the challenge, appears to be met by powerful inhibition of gastric acid secretion. A randomized trial of cimetidine, in a dose monitored to keep the gastric pH above 5, appeared to virtually eliminate the occurrence of gastroduodenal erosion and, therefore, severe bleeding in a similar group of patients.

Jean-Pierre Benhamou, M.D., Hôpital Beaujon, Clichy, France, concluded the session with a review of the Current Status of Cross-Circulation.[149] This therapy, which involves supplying the comatose patient with FHF with arterial blood from a human donor with normal liver function, while returning venous blood from patient to donor, has had a variable degree of success in the 21 reported but uncontrolled cases. In six new personal cases, in whom blood was exchanged at a rate of 50-200 ml./min. for one to three days, the author saw no evidence of clinical improvement. In order to investigate the reason for this failure, hepatectomized dogs in deep coma were cross-circulated with normal dogs and EEG improvement was used as evidence of a beneficial effect. Two different circuits were employed. EEG improvement was achieved using a systemic to portal exchange circuit at lower flow rates than were required by a systemic-systemic circuit. Nevertheless, even with the former circuit, which would be difficult to establish clinically, flow rates equivalent (in man) to 800 ml./min. were required to achieve beneficial effects. Hence, failure of clinical cross-circulation in man may principally reflect the inability to achieve adequate blood exchange rates between patient and donor.

ARTIFICIAL HEPATIC SUPPORT SYSTEMS

The introductory paper of the final day, Possible Importance of Treatment Schedule on Effectiveness of Artificial Hepatic Support Systems". The introductory paper, Possible Importance of Treatment Schedule on Effectiveness of Artificial Support Systems in FHF[3, 150-152] was given by Paul D. Berk, M.D., Liver Unit, NIH, Bethesda, MD. Poor results of conventional therapy have led to increasing interest in artificial support systems for FHF. Lacking a detailed understanding of the biochemical disturbances to be corrected by such devices, both their design and the schedule in which they are employed are largely empirical. The present study suggests that, in addition to device design, appropriate choice of schedules may be an important factor in the successful treatment of FHF by artificial hepatic support systems. Arousal of patients in coma from FHF is reported to occur 12-24 hours after charcoal hemoperfusion (HP) rather than during the procedure. This has been attributed to the depletion of a "toxin" from a slowly exchanging extravascular pool (SEEVP) such as brain or CSF. In order to investigate the effects of HP schedule on the kinetics of depletion of SEEVP's, a computer was used to simulate the effects of albumin-agarose HP on the plasma unconjugated bilirubin (UCB) concentration ([UCB]) and the mass of UCB in the SEEVP (M_{UCB}) of a patient with Crigler-Najjar syndrome, for whom baseline data including [USB] = 25 mg.% and M_{UCB} = 258 mg. were obtained from studies of radiobilirubin kinetics. Simulated effects of a single 4-hour HP indicated a continued fall in M_{UCB} after termination of treatment, with a nadir at 24 hours. Treatment 4 hr./day (standard treatment) required $\geqq$ 4 days to reduce M_{UCB} to normal ($<$ 65 mg.) and [UCB] to consistently $\leqq$ 6 mg.% whereas continuous HP normalized both by 24 hours. In contrast to standard treatment, normalization of M_{UCB} could be achieved much more rapidly (i.e. by $\leqq$ 32 hours) by various other schedules, the simplest involving only a single additional 4-hour HP midway through the first day of treatment. By analogy, this study suggests that simple alterations in the schedule of HP in FHF might accelerate depletion of the SEEVP of "toxin," thereby promoting earlier arousal, less cerebral edema and associated brain damage and more frequent survival. The results also indicate that further basic research on the pathogenesis of coma in FHF may have immediate application in the design and utilization of artificial hepatic support devices.

HEMODIALYSIS IN FHF

The first paper, Design and Properties of New Membranes: Effect on Solute Removal and Protein Loss[153-158] was given by Andre Sausse, M.D., Rhone-Poulenc Research Center, Paris, France. Use of hemodialysis in FHF is controversial. Lack of precision in appreciation of the real mass transfers (M_T) during HD may be an explanation. M_T is a function of predialysis plasma concentration (C_o), dialyzer clearance (K) and run duration (t). K depends on numerous parameters, mainly blood and dialysate flow rates (Q_B and Q_D) and dialyzer over all permeability (h_o), which in turn is a function of membrane effective area (A) and membrane permeability (h_M). The latter becomes increasingly critical as the molecular weight (MW) of the solute to be removed increases. The spectrum of h_M versus solute MW characterizes the polymer matrix of the membrane for a definite thickness. For example, h_M with Cuprophan PT 150 (thickness 21 μ) and R.P. polyacrilonitrile AN 69 (thickness 31 μ) for urea (MW = 60) are 555 and $880 \cdot 10^{-4}$ cm./mm. respectively; for Vitamin B_{12} (MW = 1,355) 41 $150 \cdot 10^{-4}$ cm./min. and for inulin (MW = 5,200) 4.2 and $40 \cdot 10^{-4}$ cm./min. Hydraulic permeabilities are 3.8 and $50 \cdot 10^{-2}$ ml./min./mm. Hg./m^2 respectively.

Since a clear understanding of what should be removed from plasma is not available, the membrane should allow the slowest possible decrease of h_M versus the increase of solute MW which does not lead to substantial mass transfer of plasma proteins. This may be obtained with a rejection coefficient above 99% for albumin (MW 65,000). Membrane performances during HD are modified by the properties of the blood-membrane interface, such as protein absorption and fibrin and/or cell deposition. It is obvious that mass transfers are smaller *in vivo* than *in vitro.*

Clinical differences between high performance HD (i.e. with membrane having a broad MW permeability spectrum) and conventional HD in FHF suggest that some high MW solutes are involved in hepatic coma. In a pure diffusion process, even with a high permeability membrane, M_T are limited to solutes below 5,000-10,000 MW. Successful removal of "toxins" is difficult to infer from simple pre- and post-HD plasma concentration comparisons, as long as body compartments, metabolic transformations and/or generation rate are not taken into account. An accurate measurement of removal may be obtained, however, from dialysate analysis. Understanding of the properties of various dialytic membranes may help indirectly to elaborate a biological model of FHF.

V. Nusinovici, M.D., Hôpital Saint-Antôine, Paris, France, next discussed the Effects of Hemodialysis with a Polyacrylonitrile Membrane (PAN HD) in FHF.[76, 158-160] Thirty-seven patients with FHF (35 in grade IV coma, two in grade III coma) underwent 161 PAN HD using a disposable RP06 hemodialyzer. Blood flow-rate averaged 200-400 ml./min.; dialysate flow-rate, 500-1,000 ml./min. Continuous EEG recording showed improvement in 29 out of 55 recorded HD. Recovery of consciousness (RC) was total in 16 patients (43.5%) of whom eight (21.5%) survived. Mean duration of coma until death or decerebration was eight days (range 1-38). In a previous series of 108 similar patients RC rate averaged 25%, survival rate 20% and mean duration of coma four days (range 1-13). RC was not related to initial factor V levels. Death in the eight patients who initially recovered consciousness was related to intercurrent complications (three cases) or lack of liver regeneration (five cases).

Mean hepatocyte volume fraction (postmortem) averaged 24% in patients who transiently recovered consciousness and 17% in patients who did not.

Plasma ammonia and unbranched amino acid (AA) levels were significantly lowered after HD (approximately 25-30%). Branched AA increased slightly although its transfer into the dialysate was not inferior to that of the unbranched AA. Transfer of ammonia and AA into dialysate was higher in patients who did recover consciousness. The initial (val + leu + isoleu)/(phe + tyr) molar ratio was significantly lower in patients without RC (0.60 vs. 0.89) and increased after PAN HD (without RC = 0.91, with RC = 1.03). Plasma free fatty acid levels did not change and no transfer into the dialysate was observed. Hence, after PAN HD for FHF with stage III-IV coma, total recovery of consciousness was observed in 43.5% of patients but survival rate was unchanged (21.5%). Plasma ammonia was significantly lowered and AA imbalance partially corrected. The precise role of PAN HD in the treatment of FHF requires further investigation.

Hemodiafiltration Methodology,[161-165] a new principle with possible application to FHF, was described by Lee Henderson, M.D., Veterans Administration Hospital, San Diego, CA. Blood cleansing by hemodialysis is inherently size discriminatory. The process is diffusion based and solutes of large molecular weight diffuse less readily than solutes of small molecular weight. In general, the clearance from blood across a hemodialyzer will be equal to or greater than that for the human kidney for solutes of up to 300 MW. The human kidney does not cleanse blood diffusively but rather by convection. The glomerulus is a hydrostatically driven ultrafilter that exhibits a filtrate to filtrand ratio for egg albumin (43,500 daltons; radius from diffusion coefficient = 28.5 A) of 0.22 and totally excludes albumin at 68,000. Hemodiafiltration, a new technic being evaluated for the treatment of uremia, deliberately mimics glomerular function in that an ultrafiltration membrane is used with a hydrostatic pressure gradient. Design of the membrane in terms of sieving coefficient was undertaken to permit uninhibited passage of insulin (5,200 MW) with virtually complete retention of albumin. There are 1.6 sq. meters of membrane area in the clinical diafilter currently being tested. Its routine application in uremic patients has been for four to six hours per treatment, with 50-100 liters of solution exchanged during that time period. Solutes of up to 5,000 daltons are cleared at a rate of 100 cc./min. during this period. Changes noted with the improved solute clearance pattern have included improvement in blood pressure control, improvement in the EEG and changes in concentration of a variety of polypeptide hormones commonly present in uremic whole blood. To the extent that FHF involves accumulation of toxins with molecular weights beyond the range effectively removed by conventional hemodialysis, hemodiafiltration may represent a reasonable approach to their removal.

SORBENTS IN ARTIFICIAL LIVER SUPPORT DEVICES

Thomas M.S. Chang, M.D., McGill University, Montreal, Canada, served as chairman of the first of two sessions on this topic. Robert L. Dedrick, M.D., NIH, Bethesda, MD, initiated this topic by discussing Hemoperfusion Through Sorbents: Introduction and Principles.[166-169] Sorbents are used extensively for industrial purification and separation processes. Their origins may be found in early recorded history and the world literature contains many thousands of individual citations. Application of sorbents to removal of endogenous and exogenous substances directly from flowing blood is a rather recent development. The use of a packed bed of sorbents for correcting biochemical abnormalities has considerable appeal because of its inherent simplicity, easy control of hemodynamic performance, large surface area for transfer, high capacity and broad spectrum of sorption. The latter results, in part, from the fact that the solute to be removed comes in direct contact with the sorbent and need not traverse a membrane. Major emphasis has been placed on activated carbon, which has usually been coated for enhanced biocompatibility and control of embolization of small particles. Such coating may produce a significant decrease in the rate of adsorption but uncoated carbon rapidly adsorbs protein so that the rate of adsorption of small molecules is also reduced. While understanding of the thermodynamics and kinetic factors related to device performance is somewhat limited, even this limited understanding has not generally been applied comprehensively to device design. Neither the effect of protein on adsorption nor the competitive nature of adsorption from complex mixtures has received adequate attention and the possibility of catalytic activity of the sorbent has been largely ignored. Careful design is quite complex because the adsorption process is intrinsically nonlinear. Device clearances may approach blood (or plasma) flow rate or be limited by diffusion effects and sorbent saturation.

Roger Williams, M.D., Liver Unit, King's College Hospital, London, England, followed, discussing HEMA Coated Charcoal Hemoperfusion and RP6 Membrane Dialysis: Comparison of Results and Biocompatibility. Initial work on artificial liver support was based on extracorporeal perfusion using activated charcoal. This was coated with an acrylic hydrogel to reduce loss of formed blood elements. Early results were encouraging as 14 (38%) of the first 37 patients treated survived and in this initial series few untoward side-effects were observed. Subsequently, however, many patients became seriously hypotensive during treatment and this was associated with a marked decrease in survival, only three of the remaining 32 patients treated with charcoal hemoperfusion surviving. The cause of the hypotension was thought to be release of vasoactive substances from platelet aggregates, which were demonstrated in blood leaving the charcoal column using the Swank screen filtration technic. A series of studies is being conducted to determine the reason for this apparent change in biocompatibility. New technics for standardizing charcoal preparations and possible approaches to improving the underlying platelet defect which develops in liver failure are being explored.

The use of hemodialysis with a polyacrylonitrile membrane (RP6, Rhone Poulenc, Paris, France) has recently been assessed. This membrane allows a similar range of small and middle molecular weight molecules to be rapidly removed from the circulation. To date, 25 patients have been treated using this membrane. Liver function in these 25, assessed by the maximum prolongation of the prothrombin time, was even worse than in the initial series of patients treated by charcoal hemoperfusion. Nine (36%) have survived. Hypotension was less pronounced, the majority of instances responding to volume expansion and platelet aggregation was seen only in one patient. During hemodialysis there was a significant removal of ammonia, free fatty acids, bile acids and, in particular, amino acids. There was an excellent correlation between the plasma phenylalanine and tyrosine levels and the patients' level of consciousness. Prospective serial measurements of these amino acids may in the future allow the optimal duration and frequency of dialysis to be determined.

In his subsequent discussion, G. Brunner, M.D. pointed out that charcoal perfusion removes epinephrine, norepinephrine, T_3, aldosterone, insulin and other desirable compounds from the blood. In the critically ill patient, depletion of some of these critical materials may have important consequences and should be considered a potentially serious disadvantage of a nonspecific adsorbent.

Thomas M. S. Chang, M.D., McGill University, Montreal, Canada, compared the above with Albumin-Cellulose Nitrate Coated Charcoal Hemoperfusion in FHF.[170-174] There is a good correlation between blood compatibility and the *in vivo* maintenance of high *in vitro* clearance characteristics of a hemoperfusion system. Thus, in the case of albumin-cellulose nitrate coated charcoal, detailed study on blood compatibility shows a minimum deposition of platelets and fibrin on its surface and a corresponding maintenance of a high *in vivo* clearance for small, large and some protein-bound molecules. In a study of albumin-cellulose nitrate coated charcoal hemoperfusion therapy in FHF with Grade IV coma (conducted in Canada, Germany and Japan) 72% of patients improved their state of consciousness and 44% survived. Neither the thrombocytopenia, platelet aggregation or hypotension reported with hydrogel-coated carbon were major problems in this series. Furthermore, in contrast to other reports using hydrogel-coated charcoal, when recovery of consciousness occurred, it usually was noted either during or very shortly after hemoperfusion. Despite its apparent efficiency in removing some toxic molecules, resulting in the rapid recovery of consciousness in some patients, this system is clearly not a complete artificial liver replacement system. It is more likely that charcoal hemoperfusion will be an important component of a more complex artificial liver assist device.

Ennio Denti, M.D., Sorin Biomedica, Saluggia, Italy concluded the session on charcoal with a paper on the Selection of Carbon and Perspectives in Hemoperfusion Support Systems in FHF.[175-179] The main reasons for coating activated carbons for use in hemoperfusion are: 1. to decrease microparticle generation, 2. to improve blood compatibility and 3. to increase the selectivity of the carbon. Any coating procedure, however, interferes to some degree with solution adsorption. The first two factors listed above were investigated using Columbia LCK, 12×28 mesh (Union Carbide Corp., U.S.A.) and BAC-MU (Mitsubishi Corp., Japan) carbons. Both carbons were selected following specific selection tests. The Columbia LCK carbon was coated with 10% regenerated cellulose. To measure microparticle generation from hemoperfusion columns containing the different carbons, a Coulter counter technic was used. The cellulose coating did not decrease the already low microparticle generation rate of the uncoated carbon. It is difficult to interpret or translate animal hemocompatibility studies, comparing coated and uncoated carbons, into the clinical situation. From toxicity, pyrogenicity and other tests, it appears, however, that properly prepared uncoated BAC-MU carbon is safe for acute clinical hemoperfusion use. For chronic treatment, as in uremia, where continual blood trauma and removal of essential high MW compounds must be restricted, it may be preferable to use coated carbon or membrane carbon containment hemoperfusion devices. Adsorption experiments confirmed that coating a carbon decreases the adsorption rate and adsorptivity of high MW compounds and to a lesser extent of middle MW compounds.

The second session on "Sorbents in Artificial Hepatic Support Systems", moderated by Roger Williams, M.D., Liver Unit, King's College Hospital, London, England, dealt with experimental adsorbents other than charcoal. George M. Abouna, M.D., Calgary, Alberta, Canada, considered the role of Resin Hemoperfusion for FHF.[180-184] To remove "neurotoxic metabolites" in hepatic encephalopathy, hemoperfusion through charged ion-exchange Dowex resins and through uncharged Amberlite resin absorbents has been widely used. The former have been largely abandoned because of their bio-incompatibility and their removal of electrolytes. The Amberlite resins used include XAD-2, XAD-4, XAD-7 and XE-336; all of which are capable of adsorbing a variety of toxic, protein-bound and lipid-soluble compounds. The following investigations were carried out to assess the value of these resins and to compare them with activated charcoal. Acute but potentially reversible hepatic necrosis was produced in 25 dogs by a technic previously described. The animals were divided into three groups: Group 1 received conventional supportive therapy only; Group 2 received hemoperfusion therapy with uncoated XAD-4 resin (Rohm and Haas); Group 3 received hemoperfusion therapy with cellulose-coated activated charcoal (Gambro). Hemoperfusion was carried out for two hours at onset of coma using a simple circuitry incorporating regional heparinization and Dacron-wool filter. Ultimate animal survival was not affected by the method of treatment. Survival was longer, however, in animals treated with charcoal than controls ($0.1 > P > 0.05$) and significantly longer than those treated with resin ($P < 0.05$). Both charcoal and resin were effective in removing various compounds such as amino acids, free fatty acids and octopamine from the plasma, although the latter was more active in removing protein-bound substances. Serious complications, however, such as thrombocytopenia, hypotension, bleeding and particle separation were common only with resin hemoperfusion. While charcoal appeared superior to resin hemoperfusion in these studies, various approaches exist for potentially improving both the biocompatibility and solute adsorption of resins. Hence, their further evaluation should be pursued.

David S. Terman, M.D., Baylor College of Medicine, Houston, TX, next discussed Extracorporeal Immunoadsorbents for Specific Removal of Circulating Immune Reactants.[185-191] There is an ever-increasing recognition of the pathogenic agents in numerous autoimmune diseases. Furthermore, immune mechanisms may play a role in the hepatocellular necrosis associated with viral hepatitis. Therefore, an attractive alternative to the use of nonspecific immunosuppressive agents would be to specifically remove pathogenic immune reactants from the circulation. Several immunoadsorbents, to which antigens, antibodies or enzymes have been covalently coupled or in which they have been physically entrapped, have been prepared. When placed in an extracorporeal circulation system, they have shown a capacity to specifically extract circulating antigen and/or antibody and to hydrolyze substrate. For example, to approach the major pathogenic system in systemic *lupus erythematosus,* deoxyribonuclease (DNAase) was covalently coupled to activated nylon microcapsules. These DNAase microcapsules demonstrated a capacity to hydrolyze nDNA circulating free or bound to antibody as an immune complex. nDNA immobilized in an immunoadsorbent composed of collodion membranes adherent to small charcoal particles showed a capacity to specifically extract circulating DNA antibodies. Canine glomerular basement membrane (GBM) antigen also physically entrapped in collodion-charcoal demonstrated a capability of specifically withdrawing circulating GBM antibodies and attenuating the development of passively induced nephrotoxic glomerulonephritis in dogs. Extended studies of canine subjects actively immunized to bovine serum albumin have shown a slow rebound of antibody production in the days following specific extraction, permitting time for repeated extracorporeal intervention to sustain antibody levels at baseline. Finally, these extracorporeal immunoadsorbents have retained their structural integrity *in vivo* and their repeated use has resulted in no immediate or long range alterations in biochemical or hematologic parameters. As such, they may represent a step toward the development of a specific approach to therapy of a broad spectrum of immunologically mediated diseases.

Bruce Scharschmidt, M.D., NIH, Bethesda, MD, next described the use of Hemoperfusion through Albumin-Agarose Gel for the Treatment of Neonatal Jaundice and of Calcium Chelating Agents and Prostaglandin E_1 to Eliminate Platelet Losses during Hemoperfusion Through Various Adsorbents.[192-195] The loss of white blood cells and particularly platelets, caused by sorbent hemoperfusion, has been a major deterrent to its clinical use. As a model of a highly selective adsorbent, Albumin-Agarose Gel (AAG) was evaluated as a means of removing bilirubin (BR) from jaundiced animals *in vivo.*

Rhesus monkeys with neonatal jaundice were subjected to AAG hemoperfusion using a specially designed apparatus which permits continuous perfusion through one of four small columns arranged in parallel, while the others are sequentially washed with saline and eluted with ethanol. Less than 15% of the animal's blood volume is required in the extracorporeal circuit at any time. The six experimental monkeys showed a significant ($P < .01$) reduction (averaging 60%) in bilirubin concentration ([BR]) after each of two perfusions at 20 and 26 hours of age. In other newborn monkeys with a higher [BR] produced by BR infusion, AAG hemoperfusion was even more effective, reducing bilirubin concentrations by as much as 87%. In contrast to previous studies in rats, however, perfused monkeys showed significant platelet losses. Subsequent studies demonstrated that addition of citrate, EDTA, or oxalate to normal, heparinized human blood essentially eliminated loss of formed blood elements during *in vitro* perfusion through uncoated charcoal, the neutral resin XAD-2, the cation exchange resin Dowex AD^R50W-X8, and AAG. Prostaglandin E_1 at a dose of 5 μg./ml. also markedly reduced platelet losses. Citrate was then used "regionally" during hemoperfusion studies through AAG, uncoated charcoal and XAD-2 in three Rhesus monkeys. Each perfusion was continued for 160 minutes. During the first 80 minutes only, citrate and calcium were infused into the column inflow and outflow lines, respectively. Results for all three perfusions were similar. During the first 80 minutes, platelet counts in the monkeys and column effluents averaged 115% and 95%, respectively, of the preperfusion value in the monkey; but fell promptly to 13% and 7% respectively, after citrate was stopped. Each of the monkeys tolerated the procedure without apparent ill effect. By markedly reducing platelet losses, use of similar technics in man may make trials of extracorporeal hemoperfusion through a variety of adsorbents clinically feasible.

Theodor Kolobow, M.D., NIH, Bethesda, MD, described an alternative approach to the biocompatibility problem, involving Continuous Ex-vivo Blood Separation with a Flow-through Centrifuge without Rotating Seals.[196] A new flow-through centrifuge without rotating seals (Adams' principle) was recently described for on-line plasmapheresis of whole blood. The separation chamber was redesigned to permit continuous plateletpheresis, leukopheresis and plasmapheresis. The new separation chamber has a single narrow spiral channel (3.5 cm. high, 0.45 cm. wide and 100 cm. long with a total prime volume of 180 ml.) with terminals for the blood inlet and packed RBC outlet and plasma, WBC and/or platelet outlets. Blood cells sediment in a radially acting centrifugal field (100-340 × g) along a distance of 0.45 cm. In this spiral configuration, blood flows "uphill" against a "g" force gradient which forces heavier cells to travel in opposite direction to plasma and lighter cells (countercurrent flow), each fraction being continuously harvested through the respective terminal. The device has been tested at up to 400 ml./min. blood flow rate. Preliminary experiments showed highly efficient separations of plasma, platelets and lymphocytes from the whole blood. Incorporation of such a device into an artificial hepatic support system may permit biochemical manipulations to be performed on plasma free of platelets and white cells, markedly reducing concerns about biocompatibility.

The potential uses of Gel Entrapped Microsomes[197-199] were discussed by Ennio Denti, M.D., Sorin Biomedioca, Saluggia, Italy. The microsomes isolated by the fractionation of liver cell homogenates contain a complex mixture of enzymes, including UDP-glucuronyl transferase, cytochrome P-450, o-demethylase, etc. It has been reported that microsomal enzyme activity in liver biopsy specimens was reduced by 50-80% in precomatose stages of liver disease. To the extent that failure of microsomal detoxification mechanisms may contribute to the syndrome of FHF, ways of utilizing functioning microsomes were investigated in an extracorporeal hepatic support system. The *in vitro* and *in vivo* use of crude microsomal preparations is limited by the rapid degradation of the membrane bound enzymes. Entrapment, however, of microsomes in an inert hydrogel achieves significant microsomal enzyme stabilization. Using immobilized, gel-entrapped microsomes, three types of experiments were conducted: 1. The *in vitro* characterization of immobilized hydroxylase, o-demethylase and UDP-glucuronyl transferase; 2. the *in vitro* biotransformation of diazepam and 3. the *in vivo* conjugation of bilirubin by intraperitoneal administration of immobilized microsomes and cofactors to Gunn rats. Preliminary results indicate that the immobilized microsomes, if assembled in an extracorporeal reactor, may function as an external detoxification system.

Gorig Brunner, M.D., University of Göttingen, West Germany, discussed Carrier Bound Microsomal Enzymes for Extracorporeal Hepatic Support.[27, 200, 201] Free phenols, free fatty acids, mercaptans and ammonia occur in the blood of patients in liver failure in high concentrations and inhibit a large number of enzymes in liver and brain. As an experimental approach to elimination of these toxins, detoxifying enzymes of rabbit liver were solubilized, purified and covalently bound to artificial carriers. Carrier-bound UDP-glucuronyltransferase is capable of eliminating phenols from blood of patients in liver failure *in vitro* and from intoxicated rabbits *in vivo*. The enzyme also conjugates bilirubin. Cytochrome-P_{450} and NADPH-cytochrome-P_{450} reductase bound to the same carrier exhibit hydroxylation activity towards hydrocarbons and fatty acids. Necessary cofactors such as UDPGA, NADPH, and phospholipid can be included into the carrier material from where they diffuse out at rates allowing maximal enzyme activity for 45-60 minutes. The carrier can be reloaded. Purified, membrane-bound detoxifying microsomal enzymes are very stable. They can be used several times and show potential as components of an extra-corporeal hepatic assist system.

Thomas M. S. Chang, M.D., McGill University, Montreal, Canada, completed this session with a detailed discussion of Microencapsulation of Multi-Enzyme Systems and Recycling of Cofactors.[202-206] Work in progress since 1957 has demonstrated that semipermeable microcapsules ("artificial cells") can be used to microencapsulate liver extract, liver cell organelles, single enzymes, or complex multienzyme systems to act on their respective substrates. The main problem is that in many enzyme systems related to the liver, there is a requirement for cofactors. In an *in vivo* situation, it would be difficult to supply the co-factor by continuous infusion. This problem may be approached by the simultaneous microencapsulation of multiple-enzyme systems, which are selected on the basis of complementary co-factor requirements whereby each enzyme generates a co-factor required by the others. The possible use of microencapsulated multienzyme systems for the recycling of ATP and NADH, as well as other co-factors, has been demonstrated. Co-factors have also been linked to soluble macromolecules to allow them to be retained within the microcapsules to continuously carry out their function. Stabilization of the multienzyme systems is obtained by microencapsulation followed by cross-linking with glutaraldehyde.

DEVICES COMBINING SORBENTS, MEMBRANES AND/OR LIVING LIVER CELLS

Paul Plotz, M.D., NIH, Bethesda, MD, moderated the final session on hepatic support systems.

Roshan Maini, M.D., University of Strathclyde, Glasgow, Scotland, discussed a Detoxification System Utilizing Both Microporous Membranes and Sorbents.[207, 208] A detoxification system for artificial liver support should remove a wide variety of substances, both free and protein-bound from blood, as well as be able to be applied for protracted periods. The core of the system proposed consists of a hemodialyser constructed with a special membrane which is porous to serum proteins while being impermeable to cellular blood components. Dialysate, composed of banked plasma, is recirculated in a closed loop through a column containing mixed sorbents. Toxins of small and middle molecular weight diffuse rapidly across the membrane, the transport of high molecular weight protein-bound toxins being increased by convective flux provided by ultrafiltration. The toxins are removed by the sorbents and excess ultrafiltered plasma is reunited with the blood circuit. Advantages afforded by this scheme are: 1. large quantities of sorbent may be used as the column is decoupled from the blood circuit; 2. small sorbent particle sizes with very large surface areas and high adsorptive capacities may be used as high pressure drops and fine filters are feasible in the absence of blood cells and 3. sorbents do not require coating with polymer membranes.

In preliminary *in vitro* experiments, a 1 m^2 Kiil hemodialyser loaded with 50 μm. thick Goretex expanded-PTFE membrane (1 μm. by 0.2 μm. pore size) has produced a sustained ultrafiltrate flow with bovine blood of 40 ml./min. at 200 ml./min. blood flow. Sorbents to be used would comprise activated carbon (removal of fatty acids, phenols, mercaptans, amino acids, unknown middle molecular weight substances), anion exchange resin (removal of bilirubin and other protein bound anions), cation exchange resins (removal of ammonia) and uncharged polymeric adsorbents (removal of bile acids and phenols). The capability of using small particle sizes will lead to better sorption kinetics for the removal of protein bound bilirubin. Endotoxin removal should also be possible by using finely ground activated carbon.

Yukihiko Nose, M.D., Cleveland Clinic Foundation, Cleveland, OH, next described Recent Developments in the Design of an Extracorporeal System for Total Hepatic Assist.[209-213] Problems of biocompatibility, low efficiency and particle carry-over remain as deterrents to extended applications of sorbent detoxification systems. Furthermore, the liver is a metabolic organ and in severe hepatic disease states, metabolic assist will also be required. For such assistance the use of viable liver tissue is being studied. To apply detoxification and metabolic support, yet prevent various well known potential problems, a membrane plasma filtration system is under development. The technic consists of the separation of plasma from whole blood by filtration through microporous membranes, the removal of toxins from the plasma by means of sorption or metabolic transformation and the reinfusion of the purified plasma into the mainstream across membranes. The membranes employed have porosities which prevent particle carry-over into the vascular system. One of the main areas requiring investigation is the need to find suitable sorbents. Efforts have concentrated on finding an effective sorbent for removal of bilirubin which, because of its high protein-binding and other physiochemical properties, is inefficiently removed by charcoal and other commonly employed materials. An experimental sorbent designated BR-601 has been found to effectively extract bilirubin from human plasma *in vitro* and from jaundiced dog blood *in vivo*. Based on these studies it is believed that practical systems involving both detoxification and metabolic assist components can be designed for the specific treatment of hepatic insufficiency.

A progress report on The Cultured Liver Cell Synthetic Capillary Artificial Liver[214-218] was presented by Carl Wolf, M.D., New York Blood Center, New York, NY. Multiple parallel hollow fibers or "artificial capillaries", made from a semipermeable membrane similar to those used for hemodialysis, support the growth of cultured cells on their exterior surfaces to tissue densities when culture medium is circulated within the fibers. The parallel fiber membrane geometry facilitates scale-up to larger units and would accommodate blood flow if extended to *in vivo* studies. Rat hepatoma cells were thus grown and were shown to perform metabolic functions such as bilirubin conjugation on the circulating medium. Glucose consumption and hepatic enzyme release into the medium were measured and the effect of membrane permeability on conjugating capacity was explored. The culture technic requires absolutely reliable constant perfusion pumps able to function for weeks, preferably using a principle which does not generate particulate debris able to occlude capillaries. Technics for morphologic examination of the fibers and cells by light microscopy and scanning and transmission electron microscopy have been developed. Animal experiments using the synthetic capillary artificial liver with normal and Gunn rats are in progress and have demonstrated bilirubin conjugation during extracorporeal hemoperfusion in the latter strain. The ultimate capabilities of such a system remain to be explored. To the extent that it can provide materials synthesized by the liver, as well as detoxifying wastes, it offers a substantial conceptual advantage over other approaches to hepatic support.

EXPERIMENTAL APPROACHES TO INVESTIGATING FHF

This session was chaired by Rudolf Preisig, M.D., University of Berne, Switzerland. Pierre Opolon, M.D., Hôpital St. Antôine, Paris, France, described the Use of Experimental Membranes to Determine the Molecular Weight of Putative Neurotoxins.[76, 158, 160] Previous work in this laboratory demonstrated: 1. prolonged wake up and significant ($P < 0.005$) EEG enhancement in 60% of pigs in coma induced by liver ischemia, following hemodialysis (HD) through a polyacrylonitrile membrane (PAN) 2. shorter survival ($P < 0.01$) and faster EEG deterioration after Cuprophan (CU) HD. Recently characteristic changes in brain neurotransmitters have been described in comatose rats during liver ischemia. The aim of this report was to study such parameters during HD with these two different membranes.

Four groups of animals were studied: 1. normal controls; 2. comatose pigs killed eight hours after liver devascularization; 3. comatose pigs killed at the same time but undergoing PAN HD from the fourth to the eighth hour after liver devascularization and 4. comatose animals undergoing CU HD at the same intervals.

Following treatment in groups 3 and 4, plasma and dialysate NH^+_4 levels were the same in both treatment groups. Regional abnormalities in brain neurotransmitter levels observed in untreated coma (group 2) were completely corrected by PAN HD but were unchanged or accentuated after CU HD. In the early phase of experimental coma, positive transfer to brain was found for threonine, serine, tryrosine, phenylalanine, histidine and valine. This was partially or completely corrected after PAN HD. Brain depletion was observed for aspartic acid, alanine (cortex) methionine (cortex), lysine, arginine and isoleucine and was not corrected after PAN HD. CU HD resulted in lower brain threonine, serine, histidine and valine without higher transfer into the dialysate. The molar ratio of (leu + val + isoleu)/phe + tyr) in plasma and brain fell during coma, and did not change after HD with either PAN or CU.

From the dialytic permeability of both membranes it is postulated that some middle molecule(s) between MW 1,500 and 5,000 is/are involved in development of encephalopathy during experimental FHF. Preliminary results with selective hemodialysis over MW 5,000 are similar to the CU HD findings, and seem to confirm this hypothesis.

An Animal/EEG System to Evaluate the Toxicity to the Central Nervous System of Abnormal Metabolites Resulting from Metabolic Diseases[219-222] was discussed by Paul Teychenne, M.D., NIH, Bethesda, MD. EEG recording during ventriculocisternal perfusion of unanesthetized rabbits has been used to assess the encephalopathic effects of the 5 carbon atom fatty acids, which accumulate in various inborn errors of metabolism. New Zealand white rabbits were anesthesized, the skull exposed and stainless steel guide tubes inserted into the bones overlying the lateral ventricles and cisterna magna. Four EEG electrodes were implanted into precisely located holes in the skull vertex. The guide tubes and EEG electrodes were left abutting on the dura without penetrating it. When the wound had healed, the rabbits were selected for perfusion. Cannulas were inserted through the ventricular and cisternal guide tubes and positioned in the lateral ventricles and cisterna magna. They were connected to a peristaltic pump and artificial CSF was perfused through the ventricles at a rate of 50 μl./min. Cerebrospinal fluid pressure was monitored continuously with an open manometer. Each fatty acid solution was infused via an ear vein at a dose of 4 mmol./kg. over a period of 12-15 minutes. Fatty acids in the CSF perfusate collected from the cisterna magna were measured by gas chromatography. The EEG obtained during the perfusion was subjected to a Fourier analysis by a computer, to give a record showing activity in a low frequency band (0.25-1.75 Hz). All the C5 acids tested induced slow wave activity in the EEG associated with a deterioration in the animal's conscious state. The increase in the slow wave activity paralleled the increase in concentration of organic acids in the CSF. The response was less marked when acids containing a double bond were infused. This technic can be used to investigate the toxic effect of abnormal metabolites which occur in various disorders of metabolism, such as those which might be involved in the genesis of hepatic coma.

Studies in an Animal Model of FHF[223-225] were described by Bennett Blitzer, M.D., NIH, Bethesda, MD. The lack of an appropriate animal model of FHF has hindered the rational design and evaluation of new therapeutic measures. In this study, galactosamine-HCl, a selective hepatotoxin, was administered in an intravenous dose of 4.25 mmol./kg. to rabbits weighing 1-2 kg. To obtain a uniform response, F_1 hybrid rabbits from a cross of two highly inbred strains (IIIVO/J × IIIC/J, Jackson Labs.) were used. Of 22 rabbits, 16 (73%) died between 22 and 41 hours after injection, four (18%) died between 48 and 89 hours and two (9%) survived despite serum biochemical evidence of massive hepatic necrosis. In nonsurvivors, death was preceded by a period of clinically obvious coma lasting 2.6 ± 0.4 (S.E.) hours. In these animals, hepatic necrosis was characterized at 18-24 hours by marked elevations of SGOT to 15,000 ± 2500 mU./ml., 5-fold elevations of alkaline phosphatase and mild hyperbilirubinemia (1.8 ± 0.2 mg.%). During this period, arterial ammonia concentration averaged three times base line, prothrombin times were markedly prolonged to at least six times base line and fibrinogen fell to undetectable levels. Changes in plasma amino acid (AA) concentrations closely paralleled those reported in human FHF, with marked increases in aromatic AA and only modest increases in branched chain AA. Arginine levels were markedly reduced. Plasma octopamine and phenylethanolamine levels did not change significantly. In a minority of animals, hypoglycemia and diminished renal function (creatinine > 3 mg.%) were present preterminally but did not appear to be major factors contributing to the development of coma. While EEG showed slight slowing in early coma, marked slow wave activity typical of hepatic coma developed suddenly in late coma. Autopsies revealed extensive hepatic necrosis in all animals and evidence of disseminated intravascular coagulation including glomerular microclots in some. Thus, this model closely resembles human FHF in its clinical, biochemical and histologic manifestations. In view of its relative reproducibility, potential for reversal and lack of hazard to personnel, it appears promising for studies of FHF.

IMPORTANCE OF CONTROLLED TRIALS IN FHF

Stuart Saunders, M.D., University of Capetown, Union of South Africa, served as chairman of this session. The EASL Acute Liver Failure Trial—A Preliminary Report on Treatment with Hydrocortisone was discussed by Niels Tygstrup, M.D., University Hospital, Copenhagen, Denmark, on behalf of the EASL Trial. The European Association for the Study of the Liver (EASL) Acute Liver Failure Trial was started 1 January 1974. Patients with encephalopathy grade II or more, caused by liver disease which had become clinically manifest less than eight weeks previously, were allocated by block-randomization (closed envelopes) to the standard treatment alone or standard treatment plus hydrocortisone. This was administered as 200 mg. intravenously twice daily either for three weeks, or until recovery from encephalopathy, or death. As of 1 January 1977, the material consisted of 40 patients from 17 centers, including 21 females and 19 males. Of these, 15 were allocated to standard therapy and 25 to hydrocortisone. Two patients of the control group and three patients of the hydrocortisone group survived for more than five weeks. ($P = 0.37$). All survivors were female ($P = 0.03$). The median age of the control group was 45 years, and that of the hydrocortisone group 30 years but the difference is not statistically significant. Hepatitis B was the presumed etiology in 20% of the controls and 60% of the hydrocortisone group ($P = 0.013$), HB_sAg-positive cases comprising 20 and 48%, respectively ($P = 0.059$). No difference was found regarding number and type of complications, degree and duration of encephalopathy, duration of clinical disease, serum bilirubin and alanine-aminotransferase levels and survival time between the groups. Because of the small sample size, the study only indicates that hydrocortisone treatments will not increase the five weeks' survival more than four times ($P_{\beta} = 0.05$). In order to exclude a smaller relative effect, much larger sample sizes are required than it appears practical to collect at this time.

Principles of Controlled Trials as They Apply to FHF[126-226]

This session was conducted by Thomas Chalmers, M.D., F.A.C.G. (Hon.), Mount Sinai School of Medicine of the City University of New York. Although hepatologists have been in the forefront of using randomized controlled trials (RCT's) for the evaluation of many problems, the area of FHF is a notable exception. Few, if any, of the many therapeutic reports summarized in a 1972 review were RCT's and none of the trials of hepatic assist devices have made any attempt at randomization. There seems to be a pervasive feeling that the basic survival rate in FHF is 15-20% and that historical experience is, therefore, a suitable guide for therapeutic effectiveness. Unfortunately, there are serious problems with the use of historical controls, since subtle changes in patient population or in the nature of the basic intensive care regimen may appreciably influence the results. Thus, the differences in survival rates reported at this meeting from Paris and London with the RP-6 Hemodialysis device may reflect such unrecognized factors, since both centers are using the same hepatic assist system. The basic rationale behind the use of controlled trials, as well as the principles both for the design of a trial and for the clinician's evaluation of published reports, have recently been reviewed. In situations like FHF in which the information to be gained from every case is precious, it is essential that all new theories be subjected to RCT's, which should begin by randomizing the first available case. Consideration should be given to the simultaneous evaluation of several therapies by trial designs incorporating various forms of multivariate analysis.

James W. Mosley, M.D., University of Southern California, Los Angeles, CA, next considered the Special Problems in Therapeutic Evaluations in FHF. He suggested that there are two misconceptions about therapeutic trials in FHF: 1. that any modality accompanied by survival of three or more patients out of 10 has been demonstrated to be worthwhile and 2. that any therapy to be worthwhile must be associated with the survival of five or more patients out of 10. Such groups of 10 patients can be useful in evaluating dose and toxicity of a medication. Nevertheless, it is only by randomly assigning 10 patients in a group of 20 to the new drug or procedure that any indication of its therapetic potential may be obtained. Such phase II studies then must be followed by one or more phase III investigations of sufficient magnitude to answer the question of benefit (or harm).

Apart from chance, the major problem in assessing a treatment from the small studies usually used for FHF is that factors of known prognostic importance may bias the outcome, even if randomization is practiced. Such characteristics may include age (but not sex), stage of encephalopathy at the time of therapeutic intervention and perhaps etiology. This problem is handled by stratification but that step is seldom feasible in small studies. In contrast, stratification is both practical and necessary for phase II evaluations. The amount of information available about those attributes that may influence outcome is still very limited. Additional studies of this aspect of the disease are needed, especially is interaction of characteristics is to be evaluated by multivariate forms of analysis.

Under most circumstances, multicenter cooperative investigations are necessary to provide sufficient numbers of patients to carry out a phase III study. No one center is likely to see enough patients to complete a stratified, randomized trial with appropriate controls, since the total number of cases of FHF in the U.S. appears to be less than 2,000/yr. The number of patients potentially available to one or even many centers, however, is very difficult to estimate. It varies with the spontaneous or sociologically determined (e.g. illicit self-injection) incidence of viral hepatitis and the changing patterns of use of drugs with a hepatotoxic potential. At all times, however, major medical centers participating in a therapeutic trial depend upon referrals from smaller hospitals to augment cases that occur in their primary patient population. For such referrals to take place, the local practitioner must know the study exists. Then, he must be convinced that the referral will be to his patient's advantage. Otherwise, he is likely to continue to provide whatever care he can himself.

A Coherent Approach to FHF and Artificial Liver Support: Lessons from the Chronic Uremia Program was given by Benjamin Burton, M.D., NIH, Bethesda, MD. Artificial kidney devices for use in man have been known since 1945. They were initially employed in the treatment of acute renal failure but since 1960, their major growth has been for use in chronic renal disease. There are now 32,000 Americans on chronic maintenance dialysis, with this figure expected to rise to 55,000 over a relatively short time. Currently it costs approximately $47,000 per patient year for this service. The growth of chronic hemodialysis programs relative to transplantation, the relative costs of research in each of these two areas versus clinical care costs versus the social costs of supporting chronically ill and often economically unproductive workers were poorly predicted, despite attempts at rational technology assessment. This field has obvious lessons for those concerned with hepatic support devices. Although it is argued that these are intended for support of acute liver failure, there will be inevitable pressures to extend this technology, if successful, to the chronic support of patients with chronic liver disease. That this pressure is inevitable is obvious, based on the relative rarity of FHF ($\leq$ 2000 U.S. cases/yr.) versus 35,000 deaths/yr. from chronic liver disease, now the fifth leading cause of death in United States males. Given a population of 10,000,000 alcoholics and the apparently increased frequency of chronic viral liver disease, there exists both a lucrative market and a medical need for a chronic hepatic support device. It is urged that the experience of the artificial kidney program be studied as a guide to the ethical, technical, social and economic problems to be faced from such technological evaluation.

CHAIRMAN'S SUMMARY—A FINAL EVALUATION

The three days of this conference served to place the problem of FHF into a broad perspective. No startling break-throughs in either understanding or management were presented. The speakers and discussants, however, clearly outlined the state of the art and brought into sharper focus the critical areas in which essential knowledge is lacking. It was noted that the incidence of human FHF appears to be decreasing. Much of the information about hepatic and cerebral function and their critical interrelationships developed from clinical and experimental studies of FHF has important implications for liver disease in general. We wish to select five areas for special mention.

The first is the miraculous new wonder-world of technology including such devices as new membranes and synthetic hollow fiber capillaries with carefully controlled molecular weight spectra; "artificial cells" in which active enzymes immobilized behind synthetic membranes can detoxify a variety of substrates while regenerating cofactors as they go along; the use of affinity chromatography for the selective removal of metabolites and immune factors from whole blood or plasma; new devices for the high-speed separation of plasma and corpuscular elements from blood and liver cell cultures as "hepatic assist" devices. The term "hepatic assist" device is strongly preferred to the more dramatic "artificial liver". The observations presented are ingenious, exciting and visionary. They are also, to a considerable extent, highly preliminary despite the fact that the fundamental ideas for the use of hemodialysis, sorbent hemoperfusion and the use of living hepatic tissue in "hepatic support devices" are all 15 or more years old. Hence, although the participants were fascinated by this amazing technology and by the basic physiologic information which was derived from it, the conversion of exciting ideas into practical and effective clinical devices is progressing very slowly.

Or is it? How will we know when we have an effective "hepatic assist device"? Considerable attention was devoted to the appropriate use of controlled trials in the development of such a device. No adequate answer was generated to the question of when, or indeed whether devices should be subject to uncontrolled "phase I" trials, or whether for each new device or modification available, the first patient and all who follow should be randomized. Each side of this question has strong advocates. The importance of the question is illustrated by the experience with charcoal hemoperfusion in the treatment of FHF. A composite of several small series employing albumin/cellulose nitrate coated charcoal reveals approximately 45% survival. Similarly, early results with methacrylate-coated charcoal hemoperfusion devices suggested approximately 40% survival. Both of these series indicate markedly better results than non-contemporaneous historical controls. Unfortunately, subsequent results with the methacrylate-coated material have been substantially less promising, with no survivors in the last 18 cases. These less favorable results were associated, however, with changes in the means of preparing and coating the charcoal. Are we to conclude that charcoal hemoperfusion is ineffective in the treatment of FHF, or merely that the inferior results are attributable to the use of different charcoal? At this point, when more than 100 patients have been treated in an uncontrolled fashion with various charcoal hemoperfusion devices, we cannot answer this question.

The neurological aspects of hepatic coma in FHF represented a second major area of interest of this conference. We are particularly grateful to the experts in the field of neurology who joined us and provided essential information not usually available to or considered by the clinical hepatologist although it is presumably available in the neurological literature. Among the many examples are the classification of brain swelling and cerebral edema, as well as the information, rendered *sotto voce*, that cerebral edema appears unequivocally to respond to steroids only when resulting from space occupying lesions; the information that the sole morphologic substrates in hepatic coma, whether acute or chronic, are lesions of the Alzheimer astrocytes, type II, which interestingly have the capacity to synthesize glutamine synthetase; that lesions of the brain stem rather than the forebrain cause loss of consciousness; that the brain has an increased affinity for ammonia in hepatic coma and that this interferes with mitochondrial/cytoplasmic hydrogen transport rather than producing failure of high energy phosphate synthesis as previously believed and that detailed statistical computer interpretation of the characteristic encephalographic alterations in hepatic coma may provide a useful parameter for both the depth and progression of the coma.

Nephrologists also shared their observations with us. They have greater and longer experience in the support of another type of metabolic encephalopathy but have not succeeded in identifying a specific uremia toxin any more than we have identified a toxin or toxins in hepatic coma. Although they emphasize urea as a major target of therapy, just as we emphasize ammonia, in both cases the emphasis may be related in part to the ease of chemical measurement rather than to a critical physiologic role for the metabolite in question.

A third aspect of the conference of great interest to us were the isolated pearls of knowledge, incidental to the main problems, which were scattered throughout all three days of the meeting. Some of this information was entirely new but some was simply not adequately appreciated. We list as examples the greater than previously expected frequency of hepatitis A in sporadic hepatitis, the cholestatic role of bile acids, the increased ammonia synthesis during steroid therapy, ligandinemia as an indicator of hepatic necrosis and finally the importance of endotoxins, which may be related to their function in the complement system, in the systemic manifestations of liver disease in general and hepatocellular necrosis in particular.

The fourth aspect of the conference of particular interest was the excellent description of the clinical, diagnostic, etiologic and prognostic factors currently recognized in fulminant hepatic failure. Although there was little that was totally new, this material was well presented and included much which we may not have previously appreciated.

The fifth and most fundamental aspect of the conference relates to the pathogenesis of fulminant hepatic failure and its various clinical manifestations. Understanding this is the prerequisite to rational therapy. Clear definitions are essential. Hepatic failure in chronic liver disease, which is often transient and episodic, differs from FHF in that its pathogenesis often has a large circulatory component. This results from the fact that a substantial fraction of hepatic blood flow bypasses the liver parenchyma through intrahepatic vascular anastomoses and extrahepatic collaterals. It is, to some extent, independent of the status of the residual liver tissue of whose function the organism is deprived. The elevated plasma amino acids in this situation appear largely to be derived from the wasting muscles and the associated encephalopathy is almost certainly due to faulty hepatic detoxification of nitrogenous compounds.

In FHF, in contrast, one must distinguish the effects of loss of liver tissue, as after hepatectomy, from those of the process of hepatocellular necrosis *per se*. The latter may result from several causes of which only a few are clearly identified. These include injurious chemicals and hypoxia, as well as an apparent role for immunologic mechanisms in viral hepatitis. Furthermore, the relationship between the hepatic and cerebral defects in FHF remains unclear, and at the moment it is useful to consider them separately. In the broad clinical spectrum of hepatic failure we may thus encounter: 1. effects of the necrotic liver cells *per se*, with increased or altered plasma amino acid levels resulting from hepatic release of these compounds (the Germans speak of Zerfall [destruction] coma) or 2. loss of liver function (Ausfall [deprivation] coma) primarily in cirrhosis but also following hepatectomy. The experimental models of liver failure so widely discussed at the meeting represent: 1. deficit of liver tissue after hepatectomy, 2. hypoxia after ingenious vascular manipulations or 3. effects of injurious agents such as galactosamine. As such, their relevance to the clinical syndrome of FHF may be somewhat tenuous, a situation magnified even further by well known species differences.

Brain dysfunction secondary to liver injury may involve: 1. alterations of the household or supporting functions of the brain, such as cerebral blood flow, mainly reflected in clinical neurological manifestations (corresponding to altered oxygen uptake or water content) and 2. the intrinsic manifestations, reflected in either behavioral changes (altered cortical functions) or levels of consciousness (disturbed brain stem functions). The interrelationship between liver failure and brain disease is not established and decades after Geiger's classic experiments on cerebral perfusion, we still do not know whether the brain depends on a substance synthesized by the liver or is injured by faulty hepatic detoxification.

The combination of acute hepatic and brain dysfunction with little hepatocellular necrosis and only minimal hyperbilirubinemia is a problem exemplified by Reye's syndrome. While many may list it under FHF, we learned that this disease is a multiorgan disturbance of high energy metabolism in the mitochondria and at least one group emphasized that hepatic function is usually recovering rapidly as the cerebral disorder proceeds to an irreversible, often fatal stage. The pathogenesis of pernicious steatosis of pregnancy is even less clear. Recent evidence suggests that the liver injury results from an excess of hepatic free fatty acids. The pathogenesis of the cerebral dysfunction in both of these syndromes is, presumably, different from that which develops rapidly in those instances of fulminant hepatic necrosis, presumably on a viral basis, in which death supervenes before severe hyperbilirubinemia develops.

The entire problem of pathogenesis is complicated by our inability to distinguish primary events from secondary consequences. We must attempt to differentiate in pathogenesis, outcome, and therapy between: 1. the liver lesion, 2. the brain disorder and 3. the secondary consequences of both in other organs.

1. Of these three murky areas, the hepatic lesion is the least well understood and here, particularly from the point of therapy, we have to distinguish the necrosis of hepatocytes from their ability to regenerate. Although necrosis has been shown to be an active sequential process, possibly depending on formation of lethal proteins or enzymes, we do not know of any pro-

cedure which inhibits the sequence. The removal of injurious toxic or immunological factors bound to the liver cells is problematic. Some 25 years ago Ivy demonstrated that no correction of any known alteration of the biochemical parameters will significantly prolong the life of the hepatectomized dog and he incriminated failure of detoxification as a central factor. This points to a defect of the microsomal biotransformation system, particularly its mono-oxygenases. Although complete blockage of the cytochrome P_{450} system is well tolerated and does not cause hepatic necrosis in animals, a vicious circle may develop in FHF in that blockage of the system by toxic agents may increase the effect of a "toxin". In this context the replacement of detoxifying enzymes by ingenious hepatic assist devices remains a promise for the future.

The only injurious processess we fully understand are hypoxia and the detergent effect of bile acids. The latter presumably plays little role in FHF since the damaged hepatocytes cease synthesizing them. Few hepatic tests indicate the fulminant nature of hepatocellular failure, although falling levels of prothrombin and complement are clinically the most useful markers. Measurement of the functional hepatic mass by galactose elimination or bile acid conjugation may help in monitoring therapy of hepatocellular failure. With regard to therapy, a few interesting but very preliminary possibilities have been suggested. One of the most appealing, based on studies in fulminant murine hepatitis, is combined insulin/glucagon administration. Amino acid administration may increase albumin synthesis but inhibits DNA synthesis illustrating the differences between somatic and regeneratory processes. In conclusion, we have no established therapy beyond meticulous conventional care to influence either hepatocellular necrosis or fulminant hepatocellular failure.

2. With regard to brain dysfunction, we propose to separate the household from the intrinsic brain functions. Decreased cerebral blood flow and oxygen uptake are characteristic for any coma. Although the role of brain edema as a primary process is controversial, the alteration of the blood brain barrier has been well illustrated by functional and by electron microscopic observations in liverless animals. The false neurotransmitter theory has had great heuristic value in focusing attention on the consequences of the altered plasma amino acid levels (increased aromatic and reduced branched amino acids) in hepatic failure. It has been suggested that the altered amino acid pattern, in and of itself, may have a deleterious effect on the blood brain barrier. The elevated tyrosine and trypotophan levels in the plasma and particularly in portions of the brain stem were emphasized and found associated with an increase, in the same locations, of octopamine as a representative of false neurotransmitters. Excessive release of tyrosine from the damaged liver and elevation of circulating octopamine due to faulty hepatic monoamino-oxidase activity are hypothetical mechanisms. The importance of false neurotransmitters was challenged by the observation that their infusion into the cerebral ventricles of rats did not interfere with consciousness. This does not prove, however, that there is not an alteration of the critical role of true or false neurotransmitters in the synapse, for injection of small amounts of neurotransmitters into specific loci in brain alters behavior radically. In addition to amino acids and false neurotransmitters, ammonia, mercaptans, phenols, free short chain fatty acids and various "middle molecules" have been incriminated but not established as cerebrotoxins. The best evidence today suggests a combination of several such compounds are involved in the development of encephalopathy. It was stated that altered electrical brain waves

do not truly reflect altered cerebral function but represent only a diagnostic "noise". This may also hold true for the biochemical markers of cerebrotoxic action, such as the elevation of alpha-keto-glutaramate in the spinal fluid.

The therapeutic procedures described; including both pharmacologic measures and hepatic assist devices, have repeatedly restored consciousness or prolonged the life of a comatose patient but have not conclusively produced sustained survival. Moreover, consciousness as an indication of improved brain stem function cannot be correlated with detectable improvement of liver function. Thus, today, the management of the brain disorder in FHF has promising leads, partially independent of the therapy of the hepatic lesion but not yet proven success.

3. Overwhelming infection and/or the failure of other systems, such as the kidney (frequently more functional than anatomic), heart and circulation, the respiratory apparatus and the hemostatic mechanisms are frequently the cause of death in FHF. The possible unfavorable effects of steroid therapy may come in here. The greatest progress in understanding and management of the specific pathophysiology has been recorded in the correction of the extrahepatic consequences of FHF. Many of the procedures, however, under consideration in management may disturb an already labile balance and thus be detrimental. A typical example is the potential induction of disseminated intravascular coagulation by activated factors present in most available clotting factor preparations. The controversies in these areas require the clinician to navigate between various clinically apparent devils and corresponding, theoretically dangerous deep blue seas.

Thus, we can currently do nothing about the process of fulminant hepatic necrosis, only a little more about the associated brain disorders and are most successful in management of other organ system alterations. Although firm statistical evidence for an increased survival rate from FHF in recent years does not exist, many assume some improvement and most clinicians credit this to better supportive management, for instance, in intensive care units. We are fascinated by the promising but still primitive and expensive hepatic assist devices, a "halfway technology" in the words of Lewis Thomas. Real progress will come, however, when we have an inexpensive "high technology" of influencing pathogenic factors by methods to be established by future basic investigations.

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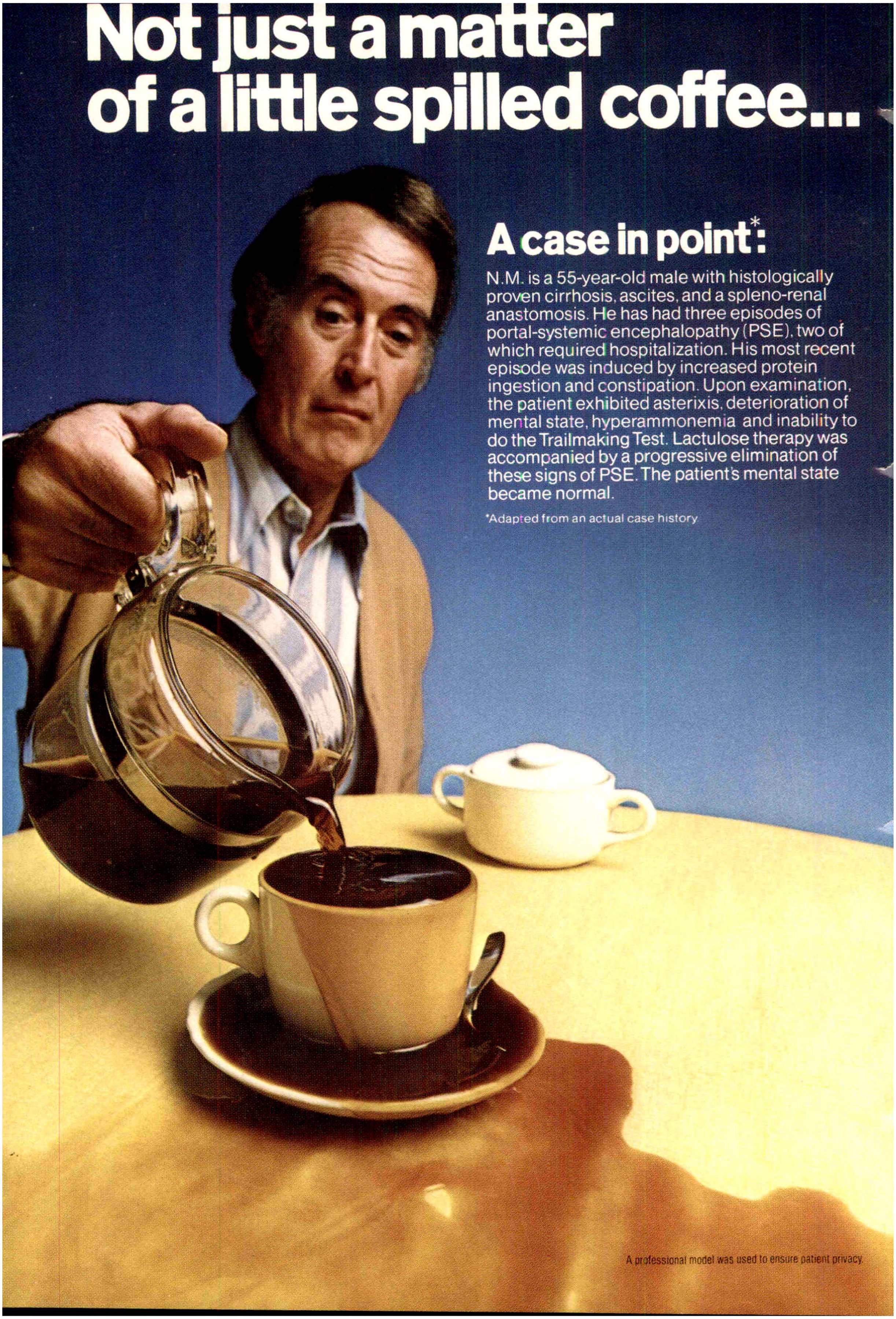

Not just a matter of a little spilled coffee...

A case in point*:

N.M. is a 55-year-old male with histologically proven cirrhosis, ascites, and a spleno-renal anastomosis. He has had three episodes of portal-systemic encephalopathy (PSE), two of which required hospitalization. His most recent episode was induced by increased protein ingestion and constipation. Upon examination, the patient exhibited asterixis, deterioration of mental state, hyperammonemia and inability to do the Trailmaking Test. Lactulose therapy was accompanied by a progressive elimination of these signs of PSE. The patient's mental state became normal.

*Adapted from an actual case history

A professional model was used to ensure patient privacy.

18.4.79

..this is portal-systemic encephalopathy (PSE)–

(Also called Hepatic Encephalopathy, Hepatic Coma.)

–a common complication of chronic liver disease.

Suspect PSE in every patient with cirrhosis.

Common early symptoms

- irritability
- euphoria
- lack of concern for others
- inappropriate behavior
- faraway look
- inversion of sleep pattern

Results of recent investigations of PSE

- Two-thirds of cirrhotic patients with portal hypertension who appeared mentally normal by conventional assessment revealed impairment of cerebral function on psychomotor testing. This dysfunction was in the same range as that in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

Treat PSE with Cephulac (lactulose) Syrup

- relieves PSE in 75% of episodes
- acts without serious adverse reactions
- lowers blood ammonia levels
- improves EEG and mental state
- permits more normal dietary protein intake
- provides an easy-to-manage means of long-term therapy

Cephulac® (lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

for the prevention and treatment of PSE in your patients with chronic liver disease

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Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose diet.

WARNINGS: *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

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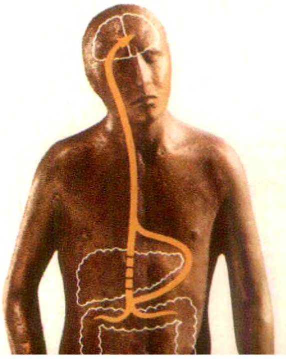

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THE American Journal OF Gastroenterology

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The Pioneer Journal of Clinical Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

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Indications / Dosage

- Duodenal Ulcer

Dosage: 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

- Pathological Hypersecretory Disorders

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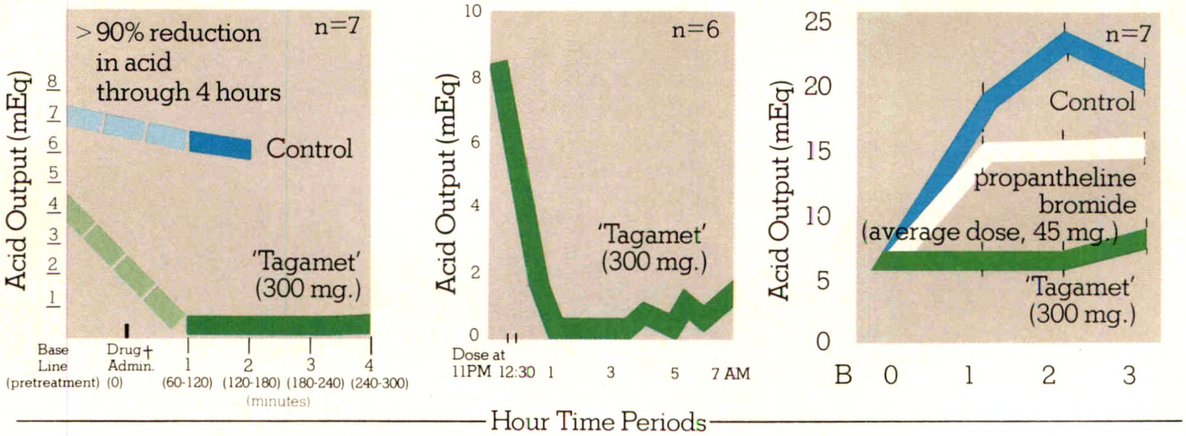
Concomitant antacids should be given as needed for relief of pain.

The 'Tagamet' Effect on Acid Secretion in Duodenal Ulcer Patients


Basal Acid Suppression*

Nocturnal Acid Suppression**

Food-Stimulated Acid Suppression*

*New England Journal of Medicine, Aug. 21, 1975

**Data on file, SK&F Medical Dept.

†Broken line indicates decrease from baseline to first measurement after drug administration.

Please see last page for brief summary of prescribing information.

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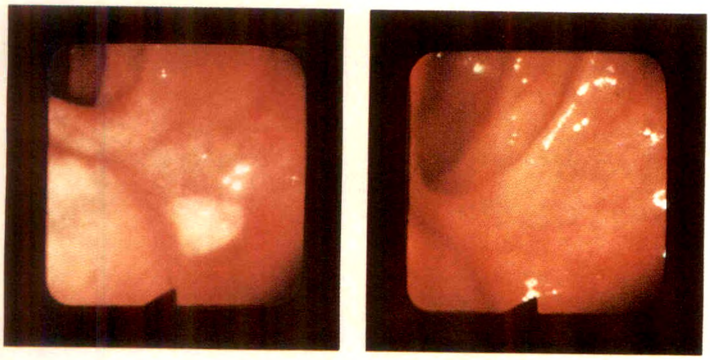
Endoscopic Examination of Duodenal Ulcer Patient on 'Tagamet' 300 mg. q.i.d.



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- **In a U.S. double-blind study* of patients with endoscopically diagnosed duodenal ulcers, 'Tagamet' (300 mg. four times a day) significantly increased the rate of healing vs. placebo at two weeks, proven endoscopically.**

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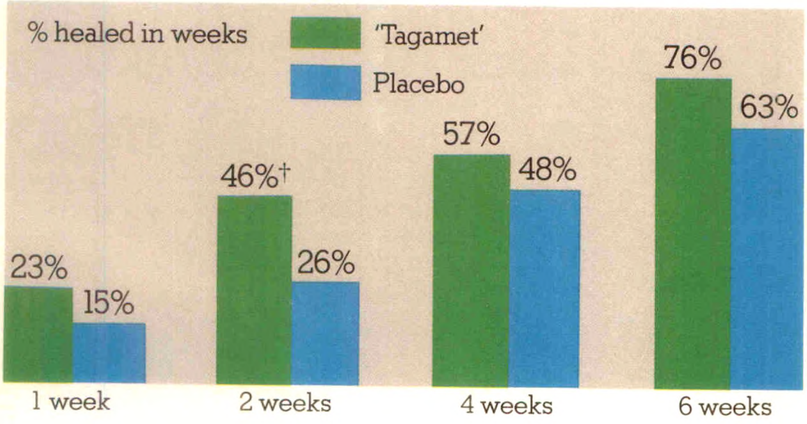

Effective Symptom Relief

- **In the same U.S. double-blind study,* global efficacy ratings of complete or marked relief were reported in 80%‡ of the patients on 'Tagamet' vs. 59% for placebo.**

*Data on file, SK&F Medical Dept.
(all patients were permitted p.r.n.
antacids for relief of pain)
†$p<0.05$
‡$p<0.01$

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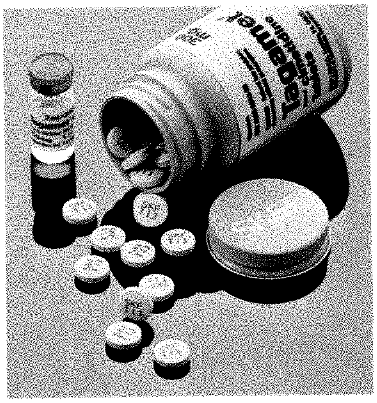

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- **Provides effective symptom relief**
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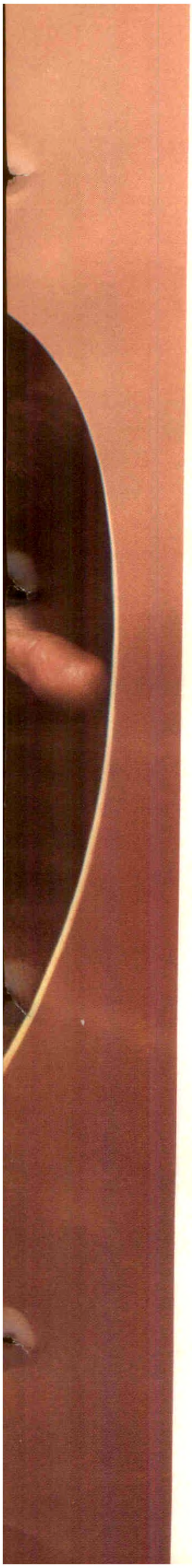

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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43rd Annual Convention, American College of Gastroenterology, The Marriott, Denver, Colo., 24-27 September 1978.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, The Marriott, Denver, Colo., 28-30 September 1978.

6th World Congress of Gastroenterology, Madrid, Spain, 5-9 June 1978.

Selected Disorders of the Colon, Postgraduate Seminar co-sponsored by the American College of Gastroenterology, the Southern Medical Association and the University of Miami School of Medicine. Bahia Mar Hotel, Ft. Lauderdale Beach, Fla., 1-3 July 1978.

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WARNINGS: In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.

Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
ADVERSE REACTIONS: Local pain or burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:

Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
HOW SUPPLIED: Single-dose 60-cc. bottles, in packages of 1 or 7, with instructions for patients.

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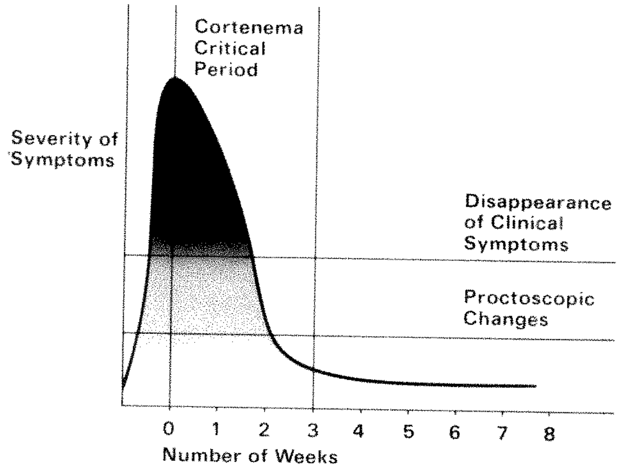

Once a diagnosis is established, Cortenema often is the only medication required for treatment of mild to moderate distal ulcerative colitis, characterized by rectal bleeding, stool abnormality (diarrhea or constipation), and diffuse mucosal ulceration and friability limited to the rectum or rectosigmoid colon.

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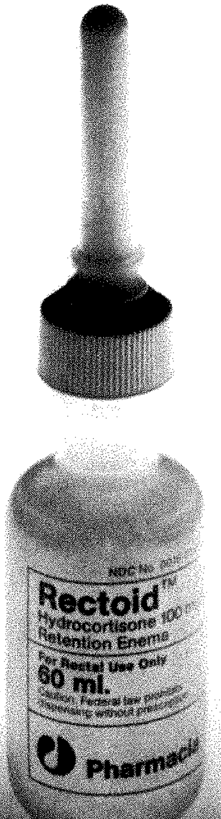

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CONTRAINDICATIONS: Systemic fungal infections; during the immediate or early postoperative period following ileocolostomy.
WARNINGS: Prolonged use may cause systemic reactions. Do not delay needed surgery while awaiting response to medical treatment. Proper insertion of the enema tip is essential to prevent rectal wall damage. Increased dosages are indicated before, during and after unusually stressful situations. Signs of infection may be masked, and new infections may appear, along with decreased resistance and decreased ability to localize infection.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Adequate human reproduction studies have not been done with corticosteroids. In pregnancy, nursing mothers or women of childbearing potential, weigh the possible benefits of the drug against the possible hazards to the mother and the embryo or fetus. Observe infants born of mothers treated during pregnancy for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention and increased excretion of potassium, requiring dietary restrictions and supplementation, may occur. All corticosteroids increase calcium excretion. *Immunization procedures, especially against smallpox, should not be undertaken in patients receiving corticosteroids, because of the possible hazard of neurological complications and lack of antibody response.* Close observation and chemoprophylaxis are indicated in patients with latent tuberculosis or tuberculin reactivity

PRECAUTIONS: Use with caution in cases of impending perforation, abscess or other pyogenic infection, fresh intestinal anastomoses, obstruction, extensive fistulas, and in the presence of active or latent peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis, or myasthenia gravis. Surgical prognosis may be impaired by increased infection hazard. Administer larger dose of appropriate antibiotics if infection is suspected. Drug-induced secondary adrenocortical insufficiency, minimized by a gradual dosage reduction, may occur with prolonged therapy. This condition may persist for months after discontinuation of therapy; therefore, hormone therapy should be reinstituted during periods of stress. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Corticosteroids exhibit an enhanced effect in patients with hypothyroidism and cirrhosis and should be used cautiously in patients with ocular herpes simplex because of possible cornea perforation. Use the lowest possible dose to control the condition and institute a gradual dosage reduction as soon as possible.

Psychic derangement may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

ADVERSE REACTIONS: Local pain or burning, rectal bleeding, and apparent exacerbations of the disease or sensitivity reactions may occur in rare instances. The following adverse reactions should be kept in mind whenever corticosteroids are given

Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis, vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurological:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirement for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
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Inflammatory Bowel Disease*

CONSIDERATIONS OF ETIOLOGY AND PATHOGENESIS

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Chicago, IL

INTRODUCTION

Although the etiology and the pathogenesis of ulcerative colitis and of Crohn's disease remain obscure, the "nonspecific" inflammatory bowel diseases in recent years have emerged as "Rosetta stones" in clarifying the nature of the gastrointestinal response to disease and the many associated biomedical disorders. Multiple etiological theories have been proposed, encompassing varied scientific disciplines but none has resolved the enigma of IBD. The purpose of this commentary is to reflect on the possible etiologic significance of various clinical and laboratory features of IBD and also to consider several concepts of current interest.

The wide range of diseases affecting the small bowel and the large bowel, including bacterial and viral infections, parasites, fungi, tuberculosis, vascular ischemia, excessive radiation, nutritional depletion and drug-induced lesions do not resemble IBD. The generally similar clinical and morphological expressions of these varied disorders reflect the limited physiological and morphological expressions of the bowel to injury. The frequency of IBD, especially among young people, most often in white populations, and the worldwide geographic distributions of ulcerative colitis and Crohn's disease reflect pathogenetic mechanisms, although their etiologic importance is not immediately apparent.

The similar clinical features and clinical course of IBD everywhere in the world, despite differing ethnic populations, environmental circumstances, dietary habits and sociocultural customs are noteworthy. For both ulcerative colitis and Crohn's disease (small and large intestine), there may be no direct correlation between the severity of the bowel disease, as demonstrated radiologically and the clinical course. Some individuals with apparently moderate involvement may have a severe and complicated course; while other patients with severe and extensive IBD radiologically seem to respond well to symptomatic management and maintain a relatively benign course.

The onset of ulcerative colitis and of Crohn's disease likewise does not provide any etiologic clues. Patients often are in good general health when IBD becomes apparent. The onset of symptoms may be gradual or abrupt. While the onset may be related chronologically to identifiable events (infections, emotional crises, drugs, fatigue, bowel operations (e.g. colostomy for diverticulitis, etc.) this temporal relationship does not establish causality; often no significant antecedent events can be described. Some patients, on careful questioning, recall the earlier excessive intake of antibiotics for respiratory and other infections, suggesting the possibility of an iatrogenic abnormality of the microflora of the gut. IBD has become more common worldwide. Whereas ulcerative colitis has increased slightly (or perhaps has plateaued), the incidence and the prevalence of Crohn's disease have risen rapidly in all parts of the world, a trend consistent with the involvement of external, environmental factors (e.g. pollutants in air, food, water or "slow viruses"). The rising dominance of Crohn's disease over ulcerative colitis is a fascinating epidemiological problem. The estimates for numbers of IBD patients in the United States range from 500,000 to 2 million people. The increasing recognition of "early" lesions of Crohn's disease and the more frequent involvement of proximal portions of the digestive tract involving the mouth, esophagus, stomach and first portion of the duodenum (aphthous ulcers, submucosal granuloma formation) with and without involvement of the distal ileum is another intriguing change in the clinical presentation of Crohn's disease.

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* Stuart Distinguished Lecture of the American College of Gastroenterology, delivered at the 42nd Annual Convention, New Orleans, LA, October 1977.

† Louis Block Distinguished Service Professor of Medicine, The University of Chicago.

IBD TISSUE REACTIONS

Ulcerative colitis is a diffuse tissue reaction, apparently beginning in the mucosa and submucosa of the colon and thus suggesting the surface action of intraluminal cytotoxic materials; although occasionally the entire bowel wall is affected immediately in a fulminating colitis. The search for intraluminal cytotoxic agents thus far has been unproductive but probably involves the excessive and the abnormal gastrointestinal aerobic and anaerobic microflora. Many of the morphological features of ulcerative colitis are consistent with an inflammatory reaction but the nature of this tissue response is not understood pathogenetically at the present time. The cellular infiltrations (polymorphonuclear cells, lymphocytes, plasma cells, eosinophils) undoubtedly represent responses to an "etiologic agent" and in this sense, they are secondary reflections rather than primary events. The immunological significance of the lymphocytic accumulations in the bowel wall in IBD is discussed later. The increased numbers of mast cells and of Paneth cells are secondary developments, though they probably contribute to the tissue reactions via the actions of the biologically active materials produced by these special cells. Numerous cytologic and cytohistochemical events in the bowel tissue of ulcerative colitis and of Crohn's disease have been observed (e.g. decreased basophilia, depletion of intracellular enzymes, overproduction of mucus, prolonged cell turnover), changes that are part of a cytological reaction to a pathogenic mechanism rather than the mechanism *per se*. Immunoperoxidase and electron microscopic examinations have demonstrated increased numbers of plasma cells, especially Ig-G cells and a relative decrease in Ig-A cells. In addition, C_3 component of complement has been demonstrated at the basement membrane of the surface epithelium and between epithelial cells; findings that have been interpreted as reflecting a local humoral immune response.

In Crohn's disease, the earliest lesions are scattered, superficial aphthoid ulcerations, resembling the canker sores of the mouth, visible in a background of normal-appearing mucosa and of interest in relation to the viral etiological hypothesis. As radiologists become more skilled in the roentgen demonstration of aphthoid ulcers in the gastrointestinal tract, "early" Crohn's lesions will be observed more often and also more frequently involving proximal areas of the gastrointestinal tract. An important feature of Crohn's disease is the focal nature of the tissue reaction, focal not only along the bowel but also in the same biopsy specimens of bowel. Other features of the Crohn's disease tissue reaction are submucosal edema and lymphatic dilatation, focal but rather diffuse distribution of the disease along the small bowel, prominent lymphoid cell accumulations and transmural involvement of the bowel wall. The lymphatic dilatation, prominent lymphoid elements, endolymphangitis, enlarged mesenteric lymph nodes and the experimentally-induced inflammation and edema of the bowel via lymphatic obstruction, all suggest involvement of the lymphatic system in the pathogenesis of Crohn's disease but the possible mechanism is unclear. Perhaps future studies will demonstrate the entrance of a "slow virus" into the lymphatic circulation of the bowel, producing the disease! The granuloma, though a useful guide to the pathological diagnosis of Crohn's disease (especially when numerous and present in the deeper layers of the bowel wall) is not specific for Crohn's disease. At least 18 or 20 infectious processes, 10 foreign body reactions and a dozen or more obscure tissue reactions (e.g. allergic granulomatosis, eosinophilic granuloma, primary biliary cirrhosis, high molecular weight polymers) are associated with granuloma formation. Furthermore, granulomas are not detectable in 30-40% of Crohn's disease tissues! Granulomas recently have been demonstrated in several extraintestinal sites in patients with Crohn's disease (bone, gastrocnemius muscle and skin), as might be expected with the systemic distribution of an etiologic agent. The injurious effects of various drugs (oral contraceptive steroids, antineoplastic agents, methyldopa, some oral antibiotics) upon the small bowel and the colon reflect the potential bowel cytotoxicity of these therapeutic agents and provide no clue to IBD. The coexistence of both ulcerative colitis and Crohn's colitis in the same patient is extremely rare, if indeed the combination exists. On the other hand, morphologic features of both entities, very occasionally, have been observed in the same resected colon; the eventual diagnosis in such instances usually is Crohn's disease, based upon current criteria. The focal nature of the process, aphthoid ulcers located over lymphoid aggregates, loose aggregates of histiocytes, right-sided predominance of the inflammation and preservation of epithelial mucin are features of Crohn's disease.

Attempts to clarify the pathogenesis of ulcerative colitis and of Crohn's disease on the basis of the discernible tissue reactions, of course, are limited by questions as to the constancy and the "specificity" of the observed changes, by the influences of antibacterial, adrenocortical steroids and other therapeutic agents, nutritional factors upon the tissue reaction, by individual differences in host response and by the likelihood that both the small intestine and the large intestine have limited tissue responses, regardless of the etiologic mechanism. Nevertheless, as more is learned of the cellular and biological events in the bowel in relation to disease, many of the presently identifiable but incompletely understood features of IBD will assume appropriate significance in the clarification of the tissue reaction now described as "nonspecific" inflammatory bowel disease.

LOCAL COMPLICATIONS

The local (colon-rectum) complications of ulcerative colitis reflect the uniqueness of the disease; a remarkable sequence of tissue reactions, as yet little understood. The problems include pericolitis, toxic dilatation of the colon, perforation, peritonitis, hemorrhage, polyps, hyperplastic filiform tumor-like tissue overgrowths, carcinoma, lymphoma, anorectal stricture, abscess and fistula formation (rectovaginal) and rectal prolapse. They occur with varying individual frequency and they profoundly influence the course of the disease and the outcome of therapy. Some individuals appear to have an exceptional vulnerability to complications; other patients, a remarkable resistance to these problems. In man, probably no other chronic bowel inflammation is associated with so many intense tissue reactions.

Carcinoma of the colon and rectum poses an especially serious challenge, pathogenetically and clinically. The neoplasm, not infrequently, is very small and flat and thus is difficult to recognize clinically. The evolution from normal to neoplastic epithelium in ulcerative colitis has not been investigated comprehensively, although the situation provides an exceptional opportunity to examine the evolution of colon-rectal cancer. Clinical and apparent tissue quiescence of the disease does not confer protective advantages over active disease in reducing the neoplastic threat. The geographic differences in the frequency of carcinoma of the colon-rectum associated with ulcerative coltis are intriguing, ranging from 0.3% in Czechoslovakia, Switzerland and France, to 3.0% in the United States, Great Britain and Sweden; differences that must involve local external, environmental factors (e.g. diet) as postulated for colon cancer generally. The biological significance of this problem also must be assessed in relation to the rising incidence of colon cancer in the Western world. Recent studies appear to support the usefulness of colonoscopy and of colonoscopic biopsies demonstrating the presence or absence of epithelial dysplasia as an index of preneoplasia. On the basis of such observations, sequential tissue studies, in cooperation with an expert pathologist, might be expected to demonstrate "a precancerous state" early enough to permit curative surgical removal of the colon and rectum. In our experience to date, the recognition of moderate or severe dysplasia by a skilled pathologist now warrants the recommendation of total colectomy and ileostomy in ulcerative colitis, since carcinoma of the colon, not recognized clinically, has been found under these circumstances. The cancer risk also includes Crohn's disease of the small intestine and of the colon, although to a lesser degree. As is typical of such associations, the neoplasm tends to develop at an earlier age than usual, often is multifocal in origin and progresses rapidly. In the small bowel, it is more likely to occur in by-passed or obstructed intestinal loops, circumstances often associated with stagnation of bowel content and anaerobic bacterial overgrowth, conditions that facilitate the intraluminal development of carcinogenic materials.

The complications of Crohn's disease of the small bowel and/or colon are dominated by a virtually relentless tendency to recurrence of the disease despite the most careful medical treatment or surgical therapy. Recurrences after small bowel resection, in my experience, range from 85-100%, depending upon the length of follow-up observation. Recurrences in the residual small bowel after total colectomy and ileostomy for Crohn's colitis, in my experience, now approximate 35%. This tendency to recurrence remains as unexplained as the primary etiology of Crohn's disease itself. Undernutrition must be an important contributory factor, because of the diminished host and local gastrointestinal defenses. Perhaps the most important factor in the frequent recurrences is the diffuse nature of Crohn's disease from its very onset, a situation not recognizable by conventional light microscopy but demonstrable now by sophisticated histological electron microscopic and cytohistochemical studies.

The tendency to recurrent fistula formation and the extension of fistulas to adjacent structures (stomach, small bowel, colon, urinary bladder, blood vessels) may be equally devastating; a vulnerability accentuated by undernutrition, overuse of steroids, initially inadequate control of the inflammatory process and by premature operation in the nutritionally-depleted, poorly prepared patient. The many local problems associated with Crohn's disease (malabsorption, Vitamin B_{12} and D deficiences, hyperoxaluria after ileal resection) reflect the vital importance of the small intestine in the normal digestive-nutritional-metabolic homeostasis of the body. The nutritional and metabolic deprivations associated with resection of the distal small intestine often are so severe as to invalid the patient indefinitely and to present even more complicated therapeutic problems than the original disease.

SYSTEMIC COMPLICATIONS

More than 100 systemic complications involving virtually every organ system in the body have been identified in IBD, a constellation of biomedical problems unmatched in any other human illness. These varied complications seem consistent with the concept of a generalized tissue vulnerability in IBD but such a concept remains speculative. While some complications antedate IBD (ankylosing spondylitis, *erythema nodosum,* iritis), most problems follow rather than precede the IBD, therefore, must be initiated via the bowel disease *per se.* Contrary to general impressions and with the possible exceptions of acute toxic arthritis and *erythema nodosum,* colectomy has an inconsistent effect upon the extracolonic manifestations of ulcerative colitis and of Crohn's disease. Since the complications are approximately the same in ulcerative colitis and in Crohn's disease of the small bowel and/or colon, the diseased bowel and its increased and abnormal aerobic and anaerobic microflora probably are the sources of some of the systemic problems associated with IBD.

The hepatic complications are numerous, including: fatty changes, hepatitis, pericholangitis, portalhepatic biliary type of cirrhosis, portal cirrhosis of the liver and portal hypertension, sclerosing cholangitis and carcinoma of the bile ducts. In addition, an increased incidence of cholelithiasis has been reported in Crohn's disease. The hepatic abnormalities are not correlated directly with the use of blood transfusions drugs, alcohol, nutritional deficiences or with other complications. Bacteriological and immunological mechanisms including the deposition of antigen-antibody immune complexes have been suggested but there is no supporting evidence as yet. Once initiated, the hepatic problems of pericholangitis and sclerosing cholangitis appear to continue almost relentlessly, uninfluenced by medication or surgery, except for the institution of adequate biliary drainage. As judged by present methods, however, bile acid metabolism appears to be normal, and the quantity of circulating lithocholic acid is not increased. The increased frequency of carcinoma of the bile ducts in IBD patients with sclerosing cholangitis is perhaps another indication of the apparent vulnerability of the IBD patient to neoplasia, although this neoplasm is rare There is no direct correlation between the occurrence and the severity of the hepatic complications and the clinical activity of the IBD. Often, the more severe hepatic problems are noted in patients with clinically mild IBD, suggesting a mechanism other than the diseased bowel, perhaps an associated immunological abnormality, including the deposition of immune complexes in the liver and biliary system.

Retardation of growth, characterized by the cessation of linear growth, lack of weight gain, retarded bone development and delayed onset of sexual maturation, occurs in from approximately 18-30% of children with IBD; more often in Crohn's disease than in ulcerative colitis. The mechanisms include: prolonged decreased intake of nutrients, increased loss of calories and nutrients through the diseased bowel and via intestinal malabsorption, the increased energy requirements of active inflammatory disease, the catabolic effects of adrenocortical steroids and perhaps deficiency of certain trace metals via the diseased bowel (e.g. zinc and possibly Co, Mn, Si, Cu). Endocrine function (thyroid, adrenal, pituitary), as well as growth hormone release and somatomedin levels, are normal. Although the therapeutic importance of oral and parenteral hyperalimentation now is well-documented and appropriately emphasizes the role of nutritional depletion, many questions remain. Why are not more IBD children growth retarded? Why do some children grow normally despite active disease and despite the continuing use of adrenal corticosteroids? Why do some children grow normally despite extensive resection of the ileum? Is growth retardation a delay in the usual adolescent growth spurt or a permanent arrest of the process and is there an impaired responsiveness of "target tissues" to normally released growth hormone? Inasmuch as bowel resection (small bowel in Crohn's disease, colectomy in ulcerative colitis) does not restore normal growth in every instance, thoughtful timing of surgery (before puberty is completed) and careful evaluation of the individual patient is required, with reference also to family growth patterns and to subtle genetic abnormalities such as the Turner syndrome and its variants, hereditary defects associated with arrested growth which infrequently may involve the IBD patient and not be correctible by bowel surgery. Nutritional depletion and malnutrition are far more common and more severe in IBD than is appreciated clinically or is revealed by conventional laboratory tests (e.g. blood counts, serum proteins). Only by careful neutron activation analyses can the *in vivo* decreases in total body nitrogen and in minerals such as potassium and calcium, in addition to vitamins and nutrients, be revealed accurately and, therefore, lead to corrective therapy.

ETIOLOGY AND PATHOGENESIS

Experimental observations:—Ulcerative colitis has not been observed to occur "spontaneously" in animals. A variety of inflammatory and ulcerative disorders of the colon have been described in dogs of various types but none resembles the human condition. Ulcerative and inflammatory lesions in the colon have been produced by a wide variety of technics in various animals. The lesions tend to be superficial, acute and transient and they disappear with discontinuance of the injurious agent. The colitis produced by the administration of carrageenan is of interest in relation to the probable involvement of the colonic microcirculation and the determinant role of *enterobacteriaceae;* the carrageenan colitis apparently cannot be reproduced in germ-free animals.

Crohn's disease also has not been reproduced experimentally. The intralymphatic injection of various sclerosing solutions, silica and talc, not surprisingly has produced inflammation and edema of the ileocecal region of the bowel but the changes do not resemble regional enteritis. The terminal ileitis of swine observed in the Scandinavian countries does not duplicate the human disease. Johne's disease, a chronic enteritis in cattle, sheep and goats caused by *Mycobacterium paratuberculosis,* likewise does not resemble Crohn's disease.

Etiologic hypotheses:—Many etiologic concepts have been proposed for ulcerative colitis, with emphasis upon infectious agents (bacteria, viruses) immune mechanisms, genetic influences and diminished host defenses but the cause remains obscure. Etiologic possibilities in Crohn's disease similarly have included bacterial and especially viral agents, immune reactions (including immune hyporesponsiveness), genetic influences and abnormalities of the lymphoid cell system and of the intestinal lymphatics. For both entities, multiple causes probably are involved. The worldwide increasing incidence of Crohn's disease, especially among young people, is of particular interest, a trend consistent with the involvement of external, environmental agents (e.g. prolonged exposure to a "slow virus", or pollutants in food and water). Thus far, no significant research of these possibilities has been undertaken.

Psychogenic factors:—The central nervous system profoundly influences the motor, secretory, absorptive and biochemical functions of the digestive system and the vascular and cellular integrity of the gastrointestinal tract and therefore significantly influences the status of the bowel in IBD. The long-known chronological association between significant emotional events and the onset and the exacerbations of ulcerative colitis is unquestioned. Nevertheless, a primary role for psychogenic factors in the pathogenesis of ulcerative colitis, a dominant hypothesis in the 1930's and 1940's, has lost appeal in recent years. Traditional psychonalytical concepts emphasizing the role of unconscious psychological problems in the pathogenesis of IBD, including childhood conflicts, personality defects, loss of a loved one and parental deprivation, dominance or incongruence, have not been supported by sufficient objective evidence and no longer seem applicable to IBD. An alleged failure of adaptive processes in particular individuals under challenging circumstances is an attractive possibility but the concept requires clarification and the suggested dynamics as yet are vague. The apparent reversibility of emotional disorders after successful medical and surgical treatment, at least in some patients, suggests that the psychogenic problems of IBD patients may be secondary events. The highly successful careers of patients who have recovered from ulcerative colitis after effective medical treatment or curative colectomy and ileostomy do not reflect a constitutionally "indecisive, inadequate" population group, as had been alleged previously. Perhaps this particular group of individuals who have negotiated their emotional problems successfully should be studied carefully, in addition to actively troubled individuals, to clarify the nature of the psychogenic difficulties.

A psychogenic basis for Crohn's disease never has been emphasized, although, as with ulcerative colitis, emotional stresses and tensions intensify symptoms, precipitate recurrences and significantly influence the clinical course of the disease. Although the relationship seems important, the problem of emotional factors in the pathogenesis of IBD is clouded by vagueness of current concepts and by limited knowledge of the neurogenic, vascular, humoral and biochemical effects of emotional stress upon the bowel. As more is learned of these physiological, biochemical and molecular events, the importance of psychogenic mechanisms in IBD probably will be renewed. There is need also for more information on the individual psychophysiological responses to stresses, to the improved understanding of individual vulnerability and individual resistance to disease in general.

Microbiological possibilities:—Many of the clinical and morphological features of ulcerative colitis are consistent with an inflammatory reaction caused by bacteria or perhaps viruses. Gut bacterial counts, aerobic and anaerobic, are increased enormously in both ulcerative colitis and Crohn's colitis. The large numbers of bacteria and their products must contribute to the inflammatory reaction in the bowel and to the "toxemia" associated with severe IBD; though this relationship awaits investigation. Bacteriological interest in ulcerative colitis focused initially upon organisms such as the diplostreptococcus; the anaerobe, *spherophorus necrophorus* and the virus of *lymphopathia venereum.* Interest today is directed to anaerobic bacteria such as Bacteroides, fastidious "variant bacteria" and to pathogenic forms of *Escherichia coli.*

Bacteriological possibilities in Crohn's disease have followed a similar pattern of limited study. Gut bacterial counts, especially anaerobes, are considerably increased. *Yersinia enterocolitica* (especially serotype 0:8) recently has been identified in some instances of acute regional enteritis and in mesenteric lymphadenitis and has been implicated in chronic Crohn's disease but further investigation is required. Fastidious gram-negative rods, tentatively classified as *Pseudomonas*-like bacteria, have been found in Crohn's disease tissue but not in ulcerative colitis and are being investigated further. Significant gaps exist in our knowledge of the gut aerobic and anaerobic microflora in IBD and little is known of the role of hemolytic coliform bacteria, bacterial endotoxins and other bacterial metabolites, the effects of long-term antibacterial therapy upon the gut microflora and the development of bacterial resistance to antibacterial agents. The mechanisms of bacterial adherence to intestinal epithelium and their subsequent penetration into the bowel wall, the role of the gastrointestinal secretory immune system in the protection of the bowel wall against bacterial invasion and the possible breakdown of immune competence at the intestinal-colonic mucosal surface are critical problems requiring investigation.

Earlier attempts to identify a pathogenic virus in IBD at the University of Chicago included tissue and serological studies of the virus of *lymphopathia venereum,* attempted transmission of IBD via the intrarectal injection of homogenates of colitis tissue in monkeys and a direct search for pathogenic enteric viruses in resected bowel tissue, all with negative results. Interest in a possible viral etiology was renewed in 1970 by Mitchell and Rees with the production of granulomas in the footpads of mice injected with homogenates of Crohn's intestinal tissue and of mesenteric lymph nodes As long as 500 days were required for evolution of the granulomatous changes, with little or no adaptation on passage. Since then numerous investigators utilizing a variety of technics have reproduced the original observations partially or completely; negative results also have been reported. A "transmissible agent" now has been identified in several laboratories, both in ulcerative colitis and in Crohn's disease bowel tissues. The agent passes a 220 mm. filter, is heat-stable, withstands freezing at −70° C but is inactivated by autoclaving. The characteristics of the "Vermont virus" suggest a picorna RNA type virus. A more recent study reported the isolation and characterization of reovirus-like agents from six of 10 patients with Crohn's disease, with cytopathic effects in Wi-38 tissue culture monolayers. The agents were related antigenically to Nebraska calf diarrhea virus of the Reoviridae family. Patients with Crohn's disease, however, did not have significant levels of antibody to Nebraska calf diarrhea virus antigen, as measured by the complement fixation test. More recently, the UCLA group has demonstrated virus particles capable of passing a 50 μm. millipore filter and also by immune electron microscopy in a continuous rabbit ileum tissue culture system containing Crohn's disease tissue. Positive results were obtained in six out of six Crohn's disease tissues and in five out of six ulcerative colitis tissues. The "viruses" obtained in London, Vermont and Los Angeles manifested uniformly similar characteristics of a picorna-type virus. Electron microscopic studies revealed a similar morphologic appearance, including a central core and an outer coat, with the ulcerative colitis agent somewhat larger in diameter than the Crohn's disease viral isolate. The animal transmission experiments and the viral tissue culture isolation studies are intriguing and potentially important. All investigators, however, acknowledge the need for more comprehensive, cooperative, confirmatory studies including the fulfillment of Koch's postulates. A method for the identification of humoral or cellular responses to these "viral agents" in IBD patients would allow in depth studies of the prevalence as well as the specificity of the alleged "viral infection" but such a resource is not yet available. Many questions, of course, remain. What is the significance of the granuloma in the animal transmission studies? Is a "viral agent" truly being transmitted? Is the picorna-type virus now identified in several laboratories a pathogen or a passenger? Are the viruses already isolated from patients with inflammatory bowel disease found in other diseases? Are they found in normal individuals? Are the propagation studies reproducible? Numerous technological problems have been encountered in the virus propagation studies but despite these and other questions, the virus possibility has emerged as one of the important areas for investigation in IBD.

Immunological mechanisms in inflammatory bowel disease:—Although an immediate type of allergic reaction in the colon to various foods, especially milk, was suggested as a possible cause of ulcerative colitis more than 50 years ago, the capability of the gastrointestinal tract to participate in or generate allergic and immunological reactions remained in doubt for many years. The possible role of a fundamental immune mechanism in the pathogenesis of ulcerative colitis was first proposed by Kirsner and Palmer in 1954 and based upon clinically impressive evidence, including the common personal and family histories of allergic disorders, the frequent association of IBD with immunologically related disorders such as aphthous stomatitis, iritis, *erythema nodosum, pyoderma gangrenosum,* autoimmune hemolytic anemia and thrombocytopenic purpura and the favorable clinical responses to ACTH and adrenal corticosteroids. All of these observations are consistent with the involvement of immunologic mechanisms in IBD. The ulcerations in the colon, observed at colonoscopy recently, in patients with systemic *lupus erythematosus,* a classic autoimmune disease, is noteworthy in this regard; the lesions are not unlike the ulcerations noted in Crohn's colitis. Recently, Crohn's disease also has been observed in association with idiopathic thrombocytopenic purpura. The very occasional association between hypogammaglobulinemia and ulcerative colitis or Crohn's disease is noteworthy in this connection in perhaps suggesting that the immunological abnormality in IBD need not represent an over reaction but rather an abnormal response and especially the loss of a protective mechanism against the disease.

Since 1954, all types of immunological reactions have been reproduced experimentally in the small intestine and the colon in our laboratory. Attempts, however, to reproduce either ulcerative colitis or Crohn's disease by varied experimental immune technics were negative. In the initial search for possible "autoantibodies" cytotoxic to colonic epithelium, many types of tissue antibodies and other "reactants" have been demonstrated in the serum of IBD patients, including ceruloplasmin, haptoglobin, orosomucoid, transferrin, alpha-2-macroglobulin, bovine albumin, antinuclear factors, antibodies to erythrocytes, gastric and small intestinal mucous cells, parietal cells, thyroglobulin, bile ductular epithelial cell and antibodies to bacteria and viruses (cmv). Since these substances are found also in non-IBD patients and in healthy controls, they cannot be implicated in the pathogenesis of IBD.

An antigen immunologically related to human colon antigen can be extracted in large amounts from the colon, cecum and feces of germ-free rats. The colon antigen is gastrointestinal-specific but not colon-specific. With this antigen, antibodies against both germ-free rat colon and against *E. coli* 014 have been demonstrated in patients with ulcerative colitis or with Crohn's disease and also in female relatives of IBD patients, themselves free of IBD. The "colon antibodies" identified thus far do not correlate with the age or sex of the patient, the extent, duration or severity of the IBD, a family history of IBD, with the presence or type of systemic complications, or with the response to steroids or azathioprine. Furthermore, the antibodies cannot be demonstrated directly in the colonic epithelium of IBD, as might be expected if they were involved in the disease process. They are not cytotoxic to fetal colonic epithelial cells in tissue culture, and they have been observed in the serum two to 10 years after total protocolectomy for ulcerative colitis. Thus, the "colon autoantibodies" appear to be secondary reflections of tissue injury and they are of no significance in the pathogenesis of IBD.

The presence of small circulating *antigen-antibody immune complexes* has been inferred in approximately one-third of patients with ulcerative colitis or with Crohn's disease from the observation of increased inhibition of antibody-induced cytotoxicity mediated by lymphocytes. Such a finding is not exclusive to IBD, since immune complexes have been reported in many disorders. Their significance is not yet known, although in several diseases they have been found in the affected tissues and, therefore, have been implicated in the secondary systemic complications of IBD (e.g. liver, skin, kidney). The "pathogenicity" of immune complexes is determined by their size, the integrity of the reticuloendothelial system, the rate of elimination of the complexes from the body and by various host factors. In IBD, it will be necesasry first to document conclusively the presence or absence of immune complexes. They may be found principally in IBD patients with particular complications, such as hepatic disease or possibly dermatological problems. In a more recent study, the presence of immune complexes in 156 patients with ulcerative colitis or Crohn's disease was sought by the detection of anticomplementary activity and I^{125}-labeled Clq precipitation. Excess anticomplementary activity was common in patients with active bowel disease and in those with extraintestinal manifestations (acute arthritis, ankylosing spondylitis and liver disease). Large complexes (Clq precipitation) were common only in patients with liver disease. The significance of these observations remains uncertain. The tests for the presence of antigen-antibody complexes are indirect and are dependent upon the binding of complexed immunoglobulin to complement. A variety of circumstances may influence the positivity and negativity of the tests, including the presence of hepatitis B antibody. Until the antigen-antibody complexes have been identified, the immunological importance of these findings would appear to be limited. On the basis of present information, the presence of immune complexes might be anticipated to be more common in IBD patients with hepatic disease and perhaps with dermatologic problems (e.g. pyoderma). The positive demonstration of circulating immune complexes in IBD would be of considerable importance in providing an opportunity for analysis of the complexes, particularly with reference to the nature of the antigen involved, the critical elusive problem that has limited understanding of the role of immune mechanisms in IBD.

Utilizing various technics, antibodies also have been demonstrated to a variety of bacteria and to the enterobacterial common antigen. Since the heterogenetic common antigen is present also in healthy people, its demonstration in IBD may have little direct etiologic significance. It may be important, however, indirectly. For example, Shorter has suggested that IBD may result from the establishment of a hypersensitivity to bacterial antigens normally present in the gastrointestinal tract. The bacterial antigens presumably gain access to the lymphoid tissues of the bowel wall and lymph nodes early in life, before the normal mucosal block to their uptake is established. The frequency of hypersensitivity to enterobacterial antigens is suggested by the observation that mononuclear cells from most normal individuals produce macrophage-inhibiting factor on exposure to a phenol water extract of *E. coli* 0110. B14. Presumably, many people are primed immunologically to react to enterobacterial antigens later, given the proper challenge. Once sensitization and challenge have occurred, the interaction of enterobacterial antigens and sensitized lymphocytes releases lymphotoxins and other biologically active mediators of inflammation, with subsequent inflammation of the bowel wall. Theoretically, when the lymphocytes interact chiefly with the membrane-associated antigens of the colonic epithelium, the features of ulcerative colitis would predominate. Cross-reacting bacterial antigens gaining access to the submucosa theoretically would produce a "granulomatous" type of inflammation, consistent with Crohn's disease, an attractive concept that, of course, requires further investigation.

In this regard, it is of interest perhaps to recall this statement from Kirsner and Palmer (1954)... "Perhaps bacteria participate in the pathogenesis of the disease initially by infection, increasing the susceptibility to further infection, and subsequently by sensitization of the bowel, as in an antigen-antibody reaction occurring among hyperreactive persons . . . Perhaps future studies should include also the concept of vulnerability of the host, a person more susceptible to ulcerative colitis because of tissue hyperreactivity, biological as well as psychogenic in origin."

Cell mediated immune responses:—Cell mediated immune responses in IBD have been studied by three principal technics: skin test, the response of circulating lymphocytes to various mitogens and by the effects of various antigens upon the *in vitro* migration of leucocytes. Skin tests are the least reliable and least informative. On the other hand, cell mediated reactions involving lymphocytes and other cells are of considerable importance in the examination of immunologically mediated tissue reactions. The immune response, in general, involves stimuli regulating the activation, suppression, maturation and modulation of lymphocyte function. Two major types of lymphocytes originate in the bone marrow, although further study continues to identify additional subtypes ("killer" cells, "helper" cells, etc.) reflecting the varied important roles of lymphocytes in immunologically mediated diseases. T-cells generally are responsible for mediating cell mediated immune reactions. B-cells are mediators of humoral immune responses but there is considerable interaction between the two types of cells. Human T-cell and B-cell lymphocytes are indistinguishable by conventional morphological criteria and their differentiation depends upon the recognition of characteristic surface (membrane) markers.

Circulating T-cell lymphocyte proportions are normal in ulcerative colitis. Decreased T-cell numbers are related to decreased total lymphocyte counts. In contrast, both T-cell proportions and T-cell numbers are diminished in Crohn's disease, perhaps because of the loss of cells via the diseased bowel, or via the sequestration of lymphocytes within the diseased intestine. In fact, T-cells are more numerous in the deeper layers of the affected bowel wall in Crohn's disease than in ulcerative colitis or control bowel tissue, an observation interpreted as reflecting a local tissue immune reaction to antigens, possibly bacterial in origin. Decreased T-cells are noted also in patients with other diseases, e.g. chronic active liver disease and active sarcoidosis. The numbers of T-cells return to normal when these diseases become quiescent, consistent with a secondary rather than a primary pathogenetic event.

Blood and lymph node lymphocytes from patients with ulcerative colitis respond normally with transformation and DNA synthesis when exposed to PHA and other mitogens. The decreased responsiveness noted very occasionally in ulcerative colitis disappears after total proctocolectomy and ileostomy, indicating the secondary nature of this transient defect. Decreased lymphocyte responsiveness to mitogens is more common in Crohn's disease, although results vary from one laboratory to another. In contrast to ulcerative colitis, the hyporesponsiveness apparently persists in some patients despite effective medical treatment or surgical removal of diseased bowel. Such observations have been interpreted as reflecting an immune "deficiency" state in Crohn's disease, although the evidence is far from conclusive. The altered T-cell and B-cell lymphocyte functions in IBD are not correlated with the activity of the disease, site of bowel involved, or duration of illness. Since there are many technological limitations in the testing of lymphocyte responses, concepts based upon such observations require much more decisive documentation.

The *in vitro* cytotoxic effect of circulating lymphocytes for colonic epithelial cells is a unique phenomenon, demonstrable in all IBD patients (ulcerative colitis, Crohn's disease) and apparently only in IBD. The cytotoxic effect is rapid, tissue specific, does not require complement, is observed also with cell-free filtrates of lymphocytes and the effect disappears within ten days after total colectomy (ulcerative colitis) or bowel resection (Crohn's disease); the phenomenon returns in Crohn's disease with recurrence of the disease. The cytotoxicity may represent an activity of T "killer" cells, the action of antibodies, largely Ig-M and possibly also Ig-G, or the influence of antigen-antibody complexes. Further investigation of this phenomenon will be of interest though the process may represent an epiphenomenon rather than an etiological event.

The leucocyte migration test examines the capacity of various tissue components to specifically inhibit the migration of peripheral circulating leucocytes and macrophages *in vitro* and is based upon the concept that antigen-induced inhibition of leucocyte migration is a correlate of cellular hypersensitivity. In this procedure, colon antigen inhibits the migration of leucocytes obtained from ulcerative colitis patients, a phenomenon observed infrequently in Crohn's disease. In contrast to "colon antibodies", the migration inhibition tests correlate directly with the clinical activity of the colitis and the effect is abolished by total proctocolectomy. These observations also are of interest but on the basis of present knowledge do not appear to have pathogenetic significance.

The many conflicting and often confusing observations reported in the literature on cell-mediated immunity in IBD reflect, in part at least, varying and limited technics, differing patient groups (as to disease activity and therapy) and variable conditions of study. Another limitation is the "nonspecificity" of the antigens employed thus far in the examination of peripheral circulating lymphocytes. The use of more "specific" or relevant" antigens (such as might be derived from the bowel itself) may yield more informative data. As Levin and Zaia have appropriately stated: "Cell-mediated immunity in human beings is devilishly complex. Synergistic and antagonistic combinations of humoral factors and mediators interact with macrophages, effector cells, helper cells and other cells with specified functions. The antigens used are crude and their specificity has been poorly documented. Thus, to assay *in vitro* one component of this complex process is rather artificial, and it is difficult to be certain of the relation between the *in vitro* test and the concurrent clinical observation." The depressed T-cell function reported recently among bereaved patients, while possibly providing a partial immunological explanation for the clinical emergence of crisis-related disorders, further emphasizes the complexities of immunologically related mechanisms in IBD.

These important limitations nothwithstanding, the lymphocyte family is of paramount importance in the pathogenesis of the tissue reactions of IBD, as in many other, if not all human illnesses. The circulating T-cell and B-cell lymphocytes, in fact, are very busy biological factories and transfer agents, bringing diverse biological materials to sites of tissue injury and inflammation. Their products include chemical mediators influencing the activities of lymphocytes, polymorphonuclear cells, eosinophils, basophils, platelets and macrophages, also lymphotoxins, skin reactive factor, growth inhibiting factors, transferrin, interferon and various types of immunoglobulins. Futher investigation of the surface markers of lymphocytes, furthermore, continues to reveal receptor sites for important components of immunological and other types of tissue reactions including immunoglobulins and immunoglobulin (Fc) components, for components of complement, hormones and vasoactive mediators (e.g. prostaglandin E, catecholamines, histamine, steroids).

THE IMMUNOLOGICAL ROLE OF THE GASTROINTESTINAL TRACT

Bowel lymphocytes:—The gastrointestinal tract is well-equipped for its important role in the immunological homeostasis of the body. The gastrointestinal immune appartus includes the lymphoid tissue (aggregated lymphoid tissue) in Peyer's patches and mesenteric lymph nodes, the lymphoid follicles beneath the epithelium in the mucosa and submucosa, the many lymphocytes and plasma cells in the bowel mucosa, the small lymphocytes within the bowel epithelium (propriolymphocytes, theliolymphocytes, interepithelial lymphocytes), the eosinophils, macrophages and mast cells and the secretory immunologic system of the gut.

Peyer's patches T-cells apparently are primed by gut antigens to provide a population of "memory T-cells" that migrate to other lymphoid sites, including the intestinal *lamina propria* and, therefore, have an important function in the host's interaction with intraluminal gut antigens. Lymphoblasts populating the *lamina propria* of the bowel probably are derived from gut-associated lymphoid tissue, primarily Peyer's patches and are precommitted to Ig-A production before becoming distributed along the mucosal surface. Lymphoid cells in Peyer's patches appear to be dependent upon intestinal antigens or other nonspecific intestinal factors such as mitogens (e.g. bacterial lipopolysaccharides) for the initial step of the activation process. Access to intestinal contents seems to be facilitated by a specialized epithelium (membranous epithelial M cells) overlying the gut-associated lymphoid tissue (Galt) in the ileum.

Increased numbers of T-cell lymphocytes are present in the bowel wall in both ulcerative colitis and in Crohn's disease but much more in Crohn's disease, especially in the submucosa and in deeper layers of the bowel wall, probably reflecting a chronic immune reaction within the diseased gut, in response to a primary antigenic (?bacterial) challenge to the bowel.

The interepithelial intestinal lymphocytes may be an intrinsic part of the epithelial layer, migrate from the *lamina propria* or originate in the blood-borne population of lymphocytes. Preliminary observations suggest that interepithelial lymphocytes are more numerous in IBD than normally and also that they may be abnormal structurally and functionally. Whereas intestinal lymphocytes from normal people respond readily to concanavalin A and poorly or not at all to PHA, the reverse has been demonstrated for intestinal lymphocytes from patients with Crohn's disease. These observations are preliminary and further study of the intestinal lymphoid tissue should be revealing, especially if more "specific" antigens (possibly derived from the bowel) are utilized in such studies.

Gastrointestinal antibodies:—Antibodies in the gastrointestinal tract are produced largely by the local lymphoid tissue but some of the antibodies originate in the blood stream. The epithelium of the small intestine and of the colon-rectum is a major source of plasma cells containing and producing Ig-A. Antigens within the intestinal lumen (dietary protein, viable bacteria) are the major antigenic stimuli. Heavy chains of each of the five major immunoglobulin classes, Ig-A, Ig-G, Ig-M, Ig-D, Ig-E, have been identified in the cytoplasm of lymphoid cells of the normal gastric, intestinal and colonic mucosa. The Ig-A-containing lymphoid cells predominate. In addition, Ig-A is localized normally in the apical portion of the cytoplasm of intestinal epithelial cells. Intestinal secretory Ig-A differs in several respects from serum Ig-A. The latter is a 7S immunoglobulin with a molecular weight of 170,000; whereas secretory Ig-A has a sedimentation coefficient of 11S and a molecular weight of 350,000. The complete role of secretory Ig-A in the normal body defenses and in disease is not defined as yet, though it participates in defending the integrity of mucous membranes against pathogenic bacteria, viruses and dietary antigens (opsonization, inhibition of bacterial growth, antiviral action, masking of antigenic sites, deterrent to the penetration of pathologic organisms and toxins). Recent studies have indicated a decreased amount of secretory Ig-A in the rectal epithelium of involved rectal mucosa in ulcerative proctitis and also in 40% of biopsies of proximal, apparently normal (light microscopy) sigmoidal mucosa, not involved in the colitis process. These findings suggest a local immunological defect in the bowel wall perhaps increasing tissue vulnerability to IBD but the preliminary observations need to be confirmed and extended. In this connection, two patients were found to have both Crohn's disease and selective Ig-A deficiency. There was no detectable serum Ig-A. Ig-A-bearing plasma cells in the *lamina propria* were diminished. Peripheral blood lymphocytes, however, showed normal numbers of Ig-A-bearing lymphocytes. The typical clinical course and histology suggested that Ig-A-mediated responses in the mucosa are not involved in the pathogenesis of Crohn's disease. Another patient with primary acquired hypogammaglobulinemia nodular lymphoid hyperplasia and giardiasis subsequently developed regional enteritis. The integrity of the intestinal and colonic mucosal epithelium as an immune barrier to the entry of intestinal antigens (e.g. enterobacterial antigens, bacterial products) is an important consideration in the pathogenesis of IBD and now is under investigation. Large numbers of immunocytes containing Ig-E also have been identified in rectal biopsies of patients with ulcerative colitis or with Crohn's disease. This finding, if confirmed, together with the increased numbers of mast cells in the colonic tissue from IBD patients, would be consistent with the concept of an antigen-induced Ig-E-mast cell interaction (as in an immediate hypersensitivity reaction), as an additional contribution to the tissue reaction in IBD.

Immunodeficiency in IBD:—Primary immunodeficiency syndromes are a heterogeneous group of diseases characterized by impairment of the B-cell system, the T-cell system or both. Infrequently, ulcerative colitis has been associated with immunodeficiency states (thymic alymphoplasia, Swiss type agammaglobulinemia), but this appears to be merely coincidence. There is no evidence for a primary immune deficiency in the usual ulcerative colitis.

An immunodeficiency state has been postulated in at least some patients with Crohn's disease because of reduced skin responsiveness to various antigens, decreased responsiveness of circulating lymphocytes to nonspecific mitogens such as PHA, con A and pokeweed mitogen, the reduced numbers of circulating T-cell lymphocytes and the absence of inhibition of leukocyte migration with intestinal antigen. Other studies, however, have produced conflicting results. This problem is not exclusive to Crohn's disease. Diminished lymphocyte reactivity also has been observed in active sarcoidosis; the response returning to normal after the active disease has subsided. Impaired lymphocyte responses also have been observed in Sjögren's disease, primary biliary cirrhosis and infectious hepatitis, among other conditions. Aside from the question of technological problems (e.g. endotoxin contamination of mitogen preparations), question arises as to the validity of attempting to assess the integrity of the total body lymphocytes and the total immune capacity of an individual on the basis of observation of a relatively few lymphocytes obtained from peripheral venous blood and by methods which do not yet allow completely pure separations of B-cell and T-cell lymphocytes. The day-to-day individual variations in lymphocyte responsiveness and the varying responses to different mitogens further reflect the limitations of current immunological technics. Perhaps lymphocyte hyporesponsiveness is related to a nutritional defect or to the presence of inhibitory substance in the blood, possibly resulting from the prior or current use of adrenocortical steroids or azathioprine or 6 MP. Such considerations and the many systemic complications direct attention to the question of host defenses and to the possibility of a fundamental tissue vulnerability to IBD and its complications. Conceivably, under circumstances of lowered host resistance, ordinarily nonpathogenic microbial agents (e.g. coliforms), anaerobes or viruses might play an unexpectedly etiologic role in the pathogenesis of IBD and at least some of its complications. Host defenses (e.g., bactericidal capacities of leucocytes, genetic regulation of immune responses) are an important consideration in the pathogenesis of inflammatory bowel disease and deserve more investigation.

Genetic factors:—Ulcerative colitis and Crohn's disease are not classic, genetically transmitted disorders. Inheritable protein, enzymatic, metabolic or chromosomal abnormalities have not been demonstrated. The circumstantial evidence, however, for a genetic influence in the pathogenesis of IBD in at least 15-20% of patients is impressive: the occurrence of IBD in three or more members of the same family spanning several generations, the increased frequency of IBD among first-degree relatives, the occurrence of IBD in monozygous twins with an increased concordance ratio and the not infrequent association of IBD with ankylosing spondylitis, an established genetic disease. The usual family relationship is one additional affected family member but five or more affected members have been observed. Usually the type of IBD (ulcerative colitis or Crohn's disease) among family members is the same as in the proband. A significant intermingling of ulcerative colitis and Crohn's disease occurs, however, in at least 25% of the families, suggesting an etiologic relationship.

The genetic mechanism possibly implicated in IBD susceptibility is not known. It does not involve a single dominant gene or a single recessive gene with complete penetrance. The most likely mechanism appears to be the combined interaction of several genes, the so-called polygenic or multifactorial type of inheritance. The genes involved remain to be identified. The genetic contribution presumably would be to facilitate a "state of readiness" in the small or large intestine, with IBD subsequently precipitated by external, environmental events, including emotional stress, bacterial or viral infections, antibiotic-induced alterations in the microflora of the bowel, and immunological reactions.

Genetically influenced susceptibility to IBD is further suggested by the association of ulcerative colitis and Crohn's disease with ankylosing spondylitis, a classic genetically-determined disease. The significant association between ankylosing spondylitis (with and without IBD) and the histocompatibility antigen HLA-B27, although not pathognomic, also is noteworthy. HLA-B27 also is strongly associated with psoriatic arthritis, Reiter's syndrome, salmonella arthropathy and acute uveitis but not with either ulcerative colitis or Crohn's disease, in the absence of ankylosing spondylitis. The histocompatibility (transplantation) genes determine the acceptance or rejection of a graft because their end product is an antigen localized on the cell membrane and hence vulnerable to the immune defenses of the host. The histocompatibility antigens thus have come to reflect individual susceptibility to certain diseases. In IBD there is no known association between specific HLA antigens (available thus far) and either ulcerative colitis or Crohn's disease, except for the positive correlation with HLA-B27 in those patients who also have ankylosing spondylitis or acute iritis. Preliminary information suggests a linkage between certain HLA haplotypes (haplotype A10, B18 genotype at the major histocompatibility locus) and the genetic transmission of a 50% defect in the functional activity of the C_2 component of complement and several IBD patients have been observed with an apparent C_2 deficiency associated with the A10, B18 haplotype. In one family a 32-year old woman with Crohn's disease and sacroilietis carried the haplotypes A10, B18 ad Aw32, B18 at the major histocompatibility locus. Serum total complement and C_2 hemolytic complement activities were undetectable, while levels of the remaining C_1-C_9 components were normal. The other members of the family (mother, father, two sisters and an only son of the patient) have either the A10, B18 or Aw32, B18 haplotype and half normal complement activity; apparently none has IBD. In another family, the parents and an only son each carried either the A10, B18 or the Aw 32, B18 HLA haplotype but in this family hemolytic complement activity was normal. The mother and the son have undergone total colectomy and ileostomy for ulcerative colitis; the father has regional enteritis. These observations are preliminary and further studies are planned but the findings are intriguing in relation to genetic influences and immunologically mediated tissue vulnerability in IBD.

In evaluating the occurrence of IBD among families, nongenetic possibilities also arise, such as common and prolonged family exposure to an environmental etiologic agent, perhaps a "slow virus". This question has been explored preliminarily in studies of lymphocytotoxic activity (LCA), as a marker of exposure to a virus in IBD families. LCA was found in 50% of IBD family members contrasting with only 4% in control families. In the IBD family group, LCA activity was noted in 40% of household contacts compared to 19% among nonhousehold contact family members. In a more recent study, lymphocytotoxic antibodies (LCA) were detected in 27 of 53 patients (51%) in contrast to 11 of 53 controls (11%) and in 23 of 53 patient spouses (43%) contrasting to three of 53 control spouses (6%). If LCA is indeed a marker of exposure to a virus, then these findings may suggest (prolonged) exposure to a virus in IBD. Much more research obviously will be required to determine whether or not the viral exposure concept is valid in IBD.

Therapeutic considerations:—Lacking knowledge of the fundamental cause (or causes) of IBD, there continues to be no truly "specific" medical treatment for IBD. Therapy at times seems irrational (oxygen, mineral water), at times hazardous (BCG, irradiation) and often confusing ["immunosuppression" (azathioprine) vs. immunological "support" (transfer factor) vs. immunological "stimulation" (levamisole)]. If immune hyporesponsiveness obtains in Crohn's disease, as has been alleged, then the apparent effectiveness of immunosuppressive medication (azathioprine, 6MP) is even more difficult to comprehend; perhaps these drugs have a different as yet unknown mechanism of action (?antiviral) in IBD.

A major flaw in the evaluation of therapeutic agents in IBD (e.g. sulfasalazine, steroids, azathioprine), is the erroneous assumption that the pharmaceutical actions of the medications "specifically" influence the nature of the disease. In fact, none of the available drugs for IBD has "specific" properties in IBD and attempts to so characterize them by statistical manipulation, including "double-blind" controlled studies, are unjustified. The therapy available for IBD is described more accurately as "facilitating" rather than "specific", facilitating in the sense of "nonspecific" control of the tissue reaction and simultaneously enhancing the host defenses of the IBD patient; as obtains with improved nutrition, concurrently with diminished tissue damage induced by steroids, for example (decreased capillary permeability and neutralization of the biochemical effects of tissue injury).

Despite these limitations, effective and occasionally "curative" measures are available for many patients in the form of comprehensive, individually designed programs. The principles of treatment are approximately the same for ulcerative colitis and for Crohn's disease. There are three principal therapeutic differences between ulcerative colitis and Crohn's disease. Crohn's disease is a more chronic type of inflammation, involving deeper layers of the bowel wall. Thus, healing can be expected to proceed more slowly in Crohn's disease than in ulcerative colitis and recovery may be slower. Consequently, anti-inflammatory therapy, including steroids, may be required for longer periods in Crohn's disease than in ulcerative colitis. The tendency for Crohn's disease to recur in the small and the large intestine after surgical resection of involved areas makes surgery less of a permanent cure in Crohn's disease than in ulcerative colitis; therefore, persistence with medical therapy despite seemingly refractory disease will be necessary more often in Crohn's disease than in ulcerative colitis. Furthermore, since Crohn's disease involves the small intestine, interference with absorptive processes and intestinal difficulties subsequently are more common and more severe than in ulcerative colitis wherein nutritional and metabolic problems occur chiefly from losses through the colon of nutrients already absorbed.

Surgery does not cure Crohn's disease (small intestine and/or large intestine). It is utilized most effectively for the management of major complications (obstruction, uncontrollable hemorrhage, intestinal perforation, abscess formation). Recurrences of Crohn's disease after operation are very high (at least 85% for the small bowel and 35% after colectomy and ileostomy). The importance of adequate nutrition in successful medical (or surgical) therapy cannot be over-emphasized. Without optimal nutrition, the patient's capacity for healing will be inadequate; host defenses will remain impaired and the response to medication such as steroids will be insufficient. Medical management must be comprehensive, individualized, coordinated and sustained and supplemented by a supportive and encouraging therapeutic attitude. Despite the limitations of present treatment, the chronicity of ulcerative colitis and of Crohn's disease, the tendency to recurrences and the numerous complications, many patients respond favorably to well-directed medical management. Approximately 20% of patients with ulcerative colitis require surgical intervention and approximately 50% of patients with Crohn's disease require surgery because of complications. Patience, perseverance, interest in the patient and detailed attention are important ingredients of successful medical treatment. No drugs currently available are likely to resolve *per se* the therapeutic challenge posed by IBD. Thoughtful scrutiny of the patient's course, perceptive clinical observation and imaginative and well-designed research, utilizing basic science as well as clinical disciplines and determined, resourceful investigators, remain the chief hope for the clarification and eventually the cure of these challenging and at times devastating diseases.

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Communication from Abroad

Treatment of Gastric Ulcer

The Randomized Clinical Trials from 1964 to 1974 and Their Impact

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Twenty-nine randomized clinical trials (RCTs) from the decade 1964-74 evaluating treatments of gastric ulcer have been analyzed. None of them fulfilled all criteria for an ideal RCT. The most frequent shortcomings were: short treatment or follow-up periods, incomplete description of the patients included, small patient samples, suboptimal experimental design, lack of double-blind testing, high number of drop-outs, less precise or less relevant types of evaluation of the treatment effect, uncontrolled ancillary treatment, or lack of statistical evaluation of the results.

The most frequently tested drug was carbenoxolone, which has been shown to be clearly effective. Judged by the effect on the recommendations in standard medical textbooks the impact of the best RCTs have been small. This situation emphasizes the need for more well-planned and performed RCTs on treatments of gastric ulcer.

INTRODUCTION

Truelove and Wright, in a review of randomized clinical trials (RCTs) in gastroenterology up to 1964,[1] concluded that strict bed-rest in hospital,[2] giving up smoking[3] and carbenoxolone (Biogastrone)[4] were of proven value in the treatment of gastric ulcer. An effect of diet,[5] intragastric milk drip containing sodium bicarbonate[6] and sedatives[2] had not been demonstrable.

The purpose of the present analysis was to evaluate RCTs on treatments of gastric ulcer during the decade 1964-1974 and their impact on current therapeutic practice. In a previous analysis RCTs on duodenal ulcer were evaluated.[7] The relevant citations were obtained from MEDLARS as previously described.[8] We accepted trials as RCTs only if: 1. patients were allocated to a treatment or a control group at random; 2. the therapeutic effect

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TABLE I

Absolute (1-7) and Relative (8-17) Requirements of RCTs on the Treatment of Gastric Ulcer

		No. of RCTs fulfilling	
		This requirement	This *and* preceding requirements
1.	a. Random allocation b. Effect evaluated by relevant variables c. GU distinguished from other ulcer	29	
2.	Ulcer diagnosed by "objective" methods	29	29
3.	Treatment schedule and dosage described	29	29
4.	Results tested (or testable) statistically	29	29
5.	Treatment or follow-up period at least 3 weeks	28	28
6.	Age, sex, or duration of history reported	25	25
7.	Group size greater than 10	24	23
8.	Adequate experimental design	24	18
9.	Double-blind testing	23	14
10.	Number of drop-outs stated	23	12
11.	Clearly defined end-points	23	10
12.	Criteria for exclusion described	22	7
13.	Statistical evaluation	20	4
14.	Ancillary treatment controlled	17	3
15.	Specification of ulcer symptoms	8	0
16.	Calculation of the type II error	0	0

was evaluated on the basis of clinically relevant variables (e.g. severity or duration of symptoms, survival, disappearance of an ulcer crater) and 3. gastric ulcer patients were distinguished from duodenal ulcer patients in RCTs evaluating both categories. Twenty-one RCTs fulfilling these criteria were obtained by the MEDLARS search. From their reference lists and from recent surveys eight additional RCTs were found. The analysis thus comprises 29 RCTs.[9-37] In 27 of these medical treatments were evaluated, one compared surgical treatments, and one compared medical with surgical treatment.

METHODOLOGIC EVALUATION

The 29 RCTs on gastric ulcer have been evaluated by the absolute and relative requirements listed in Table I. If the absolute requirements are not fulfilled, we find it difficult or impossible to make use of the results of these RCTs. Failure to meet some of the relative requirements may reduce the value of the RCT to a smaller or greater extent but in most cases this will not invalidate the results completely.

Criteria:—Criterion No. 1 simply states that the trial is an RCT on gastric ulcer.

The objective methods for the diagnosis (Criterion No. 2) were radiography alone (15 RCTs), radiography plus endoscopy (13 RCTs) (in three of these biopsies were taken from the ulcer) and surgery (1 RCT). Criteria Nos. 3 and 4 are self-explanatory. Criterion No. 5 is a very moderate one, one or more years of treatment or follow-up is not unreasonable from a clinical point of view. For all the RCTs, however, the median was four weeks and the maximum 2½ years. The description of the patients included as to age, sex and duration of ulcer history (Criterion No. 6) was incomplete in many reports. All three factors were stated in only 11 RCTs but primarily we only excluded four in which *none* of them were given. Criterion No. 7 is also very moderate. Ideally the group size should be adjusted to the type I error (risk of a false positive result), the type II error (risk of a false negative result) and the minimum difference the investigators wish to detect as significant.[38] The seven absolute requirements eliminated six or more than one-fifth of the RCTs.

The experimental design (No. 8) was considered less adequate in five RCTs, in four because the employed factorial design does not prevent the tested treatments from interacting, and in one because the cross-over design was used without an intervening treatment pause. Double-blind testing (No. 9) was not done in six RCTs. In one, however, this was motivated and presumably was without marked effect on the result. The number of drop-outs (No. 10) was not stated in six reports. In five RCTs the drop-out rate was higher than 20% of the number of included patients. Clearly defined end-points (No. 11) as complete relief from ulcer pain or disappearance of an ulcer crater, were used in 23 RCTs. In seven RCTs healing was considered complete only if confirmed by endoscopy. Fifteen RCTs used both the percentage reduction of ulcer size and the proportion of completely healed ulcers for evaluation and in six only the former showed a statistically significant difference between treatments tested. Criteria for exclusion from the trial (No. 12) were given in 22 RCTs. In eight RCTs they included age limits and the presence of more than one ulcer crater. Eight RCTs reported the percentage of patients excluded. It varied from 4-146, median 65% of the number included. Statistical evaluation (No. 13) of the results was made in 20 RCTs but only 17 stated the method used. The type I error could be evaluated from the data presented in 26 RCTs with Fisher's exact probability test or Student's t-test and in five a claimed significant positive result was not confirmed at the 5% level. Ancillary treatment (No. 14) was given but not recorded in 12 RCTs. This may cause false negative results if the ancillary treatment is effective and taken in greater amounts in the control group than in the treatment group. Specification of symptoms (No. 15) was not made in three of the 11 RCTs which also evaluated the treatment effect on ulcer symptoms. In three RCTs the consumption of antacids was used as a measure of therapeutic effect. Calculation of the type II error (No. 16), i.e. the risk of a false negative result, had not been made in any of the 14 "negative" RCTs, i.e. trials with no significant difference between treatments tested. In 13 RCTs the type II error could be calculated from the data presented. In three RCTs it was less than 5% and in five it was greater than 30%, for a therapeutic improvement of 20% and a type I error risk of 5%.

The requirements listed in Table I are ranked according to the frequency with which they are fulfilled in the RCTs studied. Some requirements with a high ranking on our list may be replaced with

TABLE II

RCTs on Carbenoxolone vs Placebo

Reference and year	Daily dosage (mg.)	Age, mean or range (years)	Female/ male ratio	Mean duration of history (years)	Duration of RCT (weeks)	Mean size of treatment and placebo group	Net mean reduction of ulcer size* (%)	Net ulcer healing rate†	
								In each RCT (%)	Cumulated (%)
10 65	300	≃ 55	0.6	≈ 2	4	23	39‡	14	
11 65	300	≃ 55	1.6	?	3	15.5	10	−5	
12 67	300-200	30-68	0.4	?	52	11	?	27	
13 69	300-150	49	0.4	7.3	5	18	?	36‡	
14** 70	300-150	24-75	0.9	?	78	20.5	?	20	
15 71	300-150	54	0	?	4	35	?	43‡	
16 72	300-150	59	0.5	?	4	22	?	54‡	
17 73	300-150	58	2.8	≈ 1	4	17	?	24	30‡

* Mean reduction of ulcer size (%) in the treatment group minus mean reduction of ulcer size (%) in the placebo group.

† Percentage of patients with completely healed ulcers in the treatment group minus percentage of patients with completely healed ulcers in the placebo group.

‡ Percentage significantly different from zero ($P = 2\alpha < 0.05$).

** RCT not double-blind

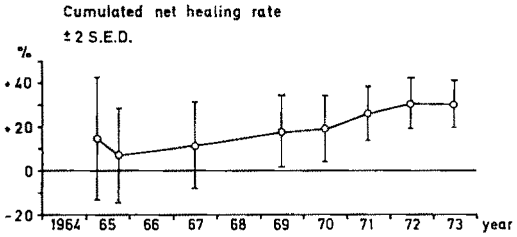

Fig. 1—Net effect of carbenoxolone on healing of gastric ulcer indicated by the cumulated net healing rate (calculated from the accumulated number of patients) ± 2 SED (standard error of the difference)[39] versus time in the period 1964-1974. Net healing rate is the percentage of completely healed ulcers in the treatment group minus the percentage of completely healed ulcers in the placebo group.[39]

others regarding RCTs dealing with other diseases.

The following analysis of different types of treatment, studied by RCTs during the decade 1964-74, only includes the 23 RCTs which meet our "absolute" requirements. In cases where the reported and the recalculated statistics differed, the later have been used.

Clinical Evaluation

Nine RCTs evaluated carbenoxolone (Biogastrone).[9-17] One RCT showed that the effect of low doses was less than that of high doses on healing of ulcers.[9] The remaining eight RCTs compared the effect of carbenoxolone with that of placebo.[10-17] Some data of these RCTs appear in Table II. No significant differences could be found between the positive and the "negative" RCTs in regard to the various data. It appears from Figure 1 that the cumulative net effect has stabilized at 30 per cent as more RCTs have been made. In duodenal ulcer patients a similar effect has been found.[7] The rather frequent side-effects of the drug can be controlled by thiazide diuretics and potassium supplementation without interfering with the effect on ulcer healing.[9]

One RCT has demonstrated that geranylfarnecylacetate is significantly inferior to carbenoxolone in promoting healing of ulcers.[18]

Two factorial experiments testing stilbestrol (Table III) were both "negative".[10, 19] Due to the design, other simultaneously tested treatments may have obscured the results. The subgroups receiving stilbestrol alone and placebo alone were small.

Three RCTs evaluated deglycyrrhizinated licorice.[20-22] One RCT compared the agent with carbenoxolone without finding any differences between the treatments.[20] Of the remaining RCTs comparing the agent with placebo (Table III) one was positive[21] and the other which used the cross-over design was "negative".[22] By addition of the results the effect on ulcer healing was not significantly different from that of placebo (Table III).

One RCT evaluating antacids found a weak antacid (dried aluminum hydroxide gel) slightly *more* effective than a potent antacid (calcium carbonate powder) in bringing about ulcer healing, but the difference was not statistically significant.[23] In spite of the lack of a placebo group, this RCT does not support the application of antacids in gastric ulcer.

The antigastrin agent proglumid has been shown in one RCT using the matched pair design to promote healing of gastric ulcers (Table III).[24]

The bismuth-protein-complex bicitropeptide has been significantly more effective than placebo in bringing about complete healing of ulcers in one RCT (Table III).[25]

One RCT has tested Cholestyramine versus placebo (Table III).[26] The agent was found to be ineffective in promoting healing of gastric ulcers.

TABLE III

RCTs ON OTHER MEDICATIONS VS. PLACEBO

Reference and year	Agent	Daily dosage	Mean age (years)	Female/ male ratio	Mean duration of history (years)	Duration of RCT (weeks)	Mean size of treatment and placebo group	Net mean reduction of ulcer size* (%)	Net ulcer healing rate†	
									In each RCT (%)	Cumulated (%)
10 65	Stilbestrol	1 mg.	≃ 55	0.2	≃ 3	5	17	16	?	
19 68		1 mg.	≃ 50	0	?	4	16	− 9	−25	−25
21 69	Deglycyrrhizinated licorice	2.28 g	≃ 55	1.7	?	4	16.5	44‡	38‡	
22 73		2.28 g.	≃ 55	1.7	≧ 3	4	34	8	− 6	8
24 70	Proglumide	1200 mg.	47	0.3	?	8	25	?	44‡	
25 71	Bicitropeptide	640 mg.	59	0.6	4.2	6	13.5	?	52‡	
26 71	Cholestyramine	12 g	53	1.3	6.8	8	17	12	6	
27 71	Proxazole	600 mg	47	0.1	?	12	20.5	?	23	
28 72	Glycopyrrolate**	O.E.D.§	50	3.0	?	3	20	17	30	
29¶ 72	Zinc sulfate	660 mg.	≃ 55	0.4	≅ 3	4	24	17	8	
29¶ 73	Vitamin A	50,000 units	≃ 55	0.4	≅ 3	4	24	−16	− 8	

* Mean reduction of ulcer size (%) in the treatment group minus mean reduction of ulcer size (%) in the placebo group.

† Percentage of patients with completely healed ulcers in the treatment group minus percentage of patients with completely healed ulcers in the placebo group.

‡ Percentage significantly different from zero ($P = 2\alpha < 0.05$).

** This RCT is not strictly placebo controlled.

§ Optimal effective dose, i.e. highest individual dose not giving side-effects.

¶ RCT not double-blind.

The antispasmodic and antiinflammatory agent proxazole has been tested versus placebo in one RCT (Table III).[27] Proxazole was slightly more effective in bringing about complete healing evaluated by endoscopy than placebo but the difference was not significantly different ($P = 0.18$).

The effect of the anticholinergic glycopyrrolate on ulcer healing was compared with that of not giving the agent in one RCT (Table III).[28] Placebo was not given in this phase of the study. The mean reduction in ulcer size was 17% higher but the percentage of completely healed ulcers was not significantly higher in the treatment group ($P = 0.10$). In a second phase of the study the effect of glycopyrrolate on prevention of ulcer recurrence was compared with that of placebo. A marginally significant difference in favor of the anticholinergic after six and 12 months was not maintained after two years ($P = 0.16$).

In a multifactorial RCT the carbenoxolone analogue BX24 (lauroyl glycyrrhetinic acid) was shown not to be better than carbenoxolone in promoting ulcer healing.[29]

The same RCT also tested zinc-sulfate and Vitamin A (Table III). Neither was found significantly superior to placebo but again this could be due to the effect of other simultaneously tested treatments.

One RCT tested vagotomy and pyloroplasty versus Billroth I gastrectomy.[30] Immediate postoperative morbidity and dumping were more frequent after gastrectomy, while reoperations and diarrhea were more frequent after vagotomy and pyloroplasty. The over all functional results (Visick grading) and the recurrence rates were not significantly different in the two groups. One big multicenter RCT compared the effect of continued medical treatment (antacids, anticholinergics, sedatives, diet) with that of surgical treatment in patients with unsatisfactory healing after a treatment period in hospital.[31] Of the 111 randomized patients only 49 were followed for two years. Of these 71% (20/28) of the surgical group and 24% (5/21) of the medical group had a satisfactory outcome without recurrence or disabling postgastrectomy symptoms. The meaning of this difference which is statistically highly significant ($P = 0.002$) is uncertain in the light of the high drop-out rate.

IMPACT

The impact of the RCTs on therapeutic practice is difficult to measure directly. The recommendations for treatments in textbooks appearing around 1964 and 1974, however, give an indication of the impact of the RCTs from the intervening period.

The medical treatments recommended by standard medical and gastroenterologic textbooks are reviewed in Table IV. It appears that antacids and to a lesser degree, anticholinergics, still are being recommended in spite of practically no support from RCTs. These drugs are still considered the mainstays of the therapy of gastric ulcer. On the other hand, carbenoxolone, which has been shown to be effective in more RCTs, is only recommended in some textbooks. The side-effects of the drug can be controlled so that these should not prevent its use in most patients. The drug is not available to the practicing physician in the United States. Drugs such as proglumid and bicitropeptide, which have been shown to be effective, are not recommended for treatment. These drugs are not mentioned in any of the textbooks examined and are not available in the United States.

The recommendations for surgical treatments have been practically unchanged during the decade.[40-45, 47-51] Most prefer gastric resection including the ulcer to

TABLE IV

RECOMMENDATIONS FOR MEDICAL TREATMENT OF GASTRIC ULCER COMPARED WITH RESULTS OF RCTs

Treatment	Results of RCTs before 1964	Recommendation for treatment 1964*	Result of RCTs 1964-1974	Recommendation for treatment 1974**
Anticholinergics	no RCT	(+)	–	(+)
Antacids	–	+	–	+
Diet	–	+	no RCT	(+)
Bed-rest	+	+	no RCT	(+)
Sedatives	–	+	no RCT	(+)
Giving up smoking	+	+	no RCT	+
Carbenoxolone	+	none	+	(+)
Stilbestrol			–	–
Deglycyrrhizinated licorice			–	none
Proglumide			+	none
Bicitropeptide			+	none
Cholestyramine			–	none
Proxazole			–	none
Zinc sulfate			–	none
Vitamin A			–	none

* Based upon references 40-42.
** Based upon references 43-48.
+ Cumulated result of RCTs positive, i.e. $P = 2\alpha < 0.05$, or treatment recommended, respectively.
– Cumulated result of RCTs 'negative', i.e. $P = 2\alpha > 0.05$, or treatment not recommended, respectively.
(+) Treatment recommended in some textbooks but not in other textbooks.

pyloroplasty and vagotomy or antrectomy as some carcinomas may be missed in the latter procedures even if operative biopsy is performed.

PERSPECTIVES

The analysis has revealed that the RCTs on treatment of gastric ulcer in the decade 1964-74 are very heterogenous. They have included small and sometimes rather highly selected samples of the gastric ulcer population. The diversity as to design, blinding, selection of patients, duration of treatment or observation periods, type of evaluation and interpretation of the results indicates that many RCTs were not sufficiently well planned or performed. The contribution of the RCTs to our present knowledge on the effect of the various treatments has been rather small and the information obtained from the best RCTs has had little impact on current therapeutic practice which is predominantly based on uncontrolled observations. The explanations for these discrepancies are numerous. Results from individual RCTs are often contradictory and it may be necessary to combine results of many RCTs to get a clearer picture. The RCTs are few in number[8] and some may be overlooked because they "drown" in the flood of uncontrolled therapeutic information. The results of a RCT may not be accepted if deserved criticism can be raised against it but even if it is beyond methodological criticism the results may be neglected if they clash with "clinical experience" or uncontrolled "knowledge". Doctors may be reluctant to leave treatments proved to be ineffective in RCTs if their patients think they help, even if this is a pure placebo effect.[52] To improve the situation, more well planned and well conducted RCTs must be produced and the results should be communicated more effectively to the medical profession. Future RCTs should include larger[38] and less selected samples of gastric ulcer patients, in whom the diagnosis is confirmed and the effect evaluated by gastroscopy. The duration of RCTs should be longer and the results should be evaluated statistically for both type I and type II errors.

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Effect of a New Antacid on Basal and Meal-stimulated Gastric Secretion

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Our study of the comparative neutralizing effectiveness of four antacids on the acidity and pH of the basal gastric secretion in 32 patients showed that using the conventional doses of two tablets of Rolaids®, two tablets of Di-Gel®, 15 ml. of Maalox liquid® or two tablets of Conquel®, they are equal in their acid neutralizing capacity. The duration of action lasted for 45-60 minutes. Conquel, in a dose of two tablets, was a potent buffer for the peptone-meal stimulated secretion. The duration of action lasted for longer than two hours.

Antacids have played a traditional role in the treatment of acid-peptic disease. Antacid, by definition, is any substance capable of lowering the acidity of the gastric contents. From the clinical standpoint, the ideal antacid for the treatment of patients with acid-peptic disease would be one that acts rapidly and produces effective neutralizing results when administered in small dose. In addition, it should be palatable, at low cost and harmless.

The aim of this investigation is to study the effect of a new antacid, Conquel®, on basal and meal-stimulated gastric secretion in man. This new antacid tablet is palatable, softer, and creamier than other antacid tablets.

MATERIAL AND METHODS

Each 2.5 gm. of Conquel® tablet contains 375 mg. of FMA-40,[1] an active ingredient which contains an average of 207 mg. of aluminum hydroxide and 101 mg. of magnesium carbonate co-dried gel. This combination yields an antacid in dry form with an average MgO/Al_2O_3 ratio of 0.37. Other major ingredients consist principally of sucrose (50%), partially hydrogenated vegetable fat (25%) and moisture (8%). Each tablet contains an average of 14 mg. of sodium with a maximum of 22 mg.

The antacid properties of aluminum hydroxide-magnesium carbonate dried gel were elevated in vitro by Beckman,[2] who found "that its buffering action is very rapid and prolonged in the optimum pH range of 3-5. It compares favorably in this respect with reactive liquid aluminum hydroxide gels."

Comparative study of Conquel with three antacids on basal gastric secretion:—This study was conducted at two different stations. At each station, 16 patients were selected. Each patient served as his own control and four studies of gastric secretion with four different antacids were completed in each patient. All four antacids were randomly allocated to each patient such that the order in which antacids were taken conformed to a Williams cross-over design.[3] The type and dose of these four

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TABLE I

EFFECT OF CONQUEL, MAALOX, ROLAIDS OR DI-GEL ON THE FREE ACIDITY AND pH OF THE BASAL GASTRIC SECRETION IN 16 PATIENTS AT STATION I

Type of antacid		Basal (minutes)				Postantacid (minutes)						
		15	30	45	60	10	20	30	45	60	75	90
Free acidity (mEq./l.)												
Conquel	mean	29	29	29	31	2*	2*	6*	14*	23	22	27
	S.D.	12.0	10.6	13.1	10.5	5.3	3.9	7.5	14.2	15.0	16.0	23.7
Maalox	mean	26	28	29	28	2*	2*	10*	18*	28	33	43
	S.D.	10.8	10.1	11.9	9.6	3.4	4.4	10.7	15.7	16.0	15.9	15.3
Rolaids	mean	33	35	38	39	7*	6*	10*	20*	37	36	39
	S.D.	20.1	16.2	20.3	20.7	14.3	9.3	15.8	17.5	20.0	14.3	18.3
Di-Gel	mean	30	32	34	35	7*	7*	12*	17*	32	39	40
	S.D.	18.9	15.5	20.8	21.1	8.9	9.5	15.1	13.2	14.6	19.7	19.1
pH												
Conquel	mean	1.7	1.7	1.7	1.7	4.7*	4.6*	3.7*	2.8*	2.1*	2.1*	2.0*
	S.D.	0.34	0.19	0.22	0.21	1.67	1.84	1.64	1.45	0.72	0.71	0.52
Maalox	mean	1.8	1.8	1.7	1.7	4.5*	4.3*	3.3*	2.5*	1.8	1.6	1.5
	S.D.	0.38	0.29	0.22	0.25	1.50	1.65	1.82	1.01	0.47	0.31	0.16
Rolaids	mean	1.7	1.6	1.6	1.6	4.2*	4.2*	3.7*	2.3*	1.7	1.7	1.7
	S.D.	0.34	0.30	0.29	0.26	2.02	1.89	1.84	0.66	0.48	0.52	0.36
Di-Gel	mean	1.8	1.7	1.7	1.7	3.6*	3.7*	3.1*	2.5*	1.7	1.6	1.7
	S.D.	0.42	0.41	0.33	0.32	1.70	1.60	1.37	1.27	0.27	0.32	0.43

* $P < 0.05$ between the mean values of postantacid and basal periods.

antacids were: two tablets of Conquel, 15 ml. of Maalox® liquid preparation, two tablets of Rolaids® and two tablets of Di-Gel®.

Each patient fasted for 14 hours and received no medicaments the day before the test. A nasogastric tube (16F) was introduced orally or nasally under fluoroscopic observation at Station I so that its tip rested in the most dependent portion of the stomach. At Station II, x-ray or fluoroscopy was resorted to only if there was a question of the position of the tube. The patient remained in a sitting position and was instructed to expectorate all saliva. The stomach was emptied completely and the study began after a 20-minute collection of gastric juice. Basal gastric secretion was collected at 15-minute intervals for one hour by means of a vacuum pump with continuous suction, with 10-second interruptions each minute. The antacid and 30 ml. of water were then ingested orally. Four-ml. samples of gastric juice were then taken at 10-minute intervals for 30 minutes, followed by 15-minute intervals for 60 minutes.

The volume, pH, free (pH 3.5) and total (pH 7.0) acidity of each sample of gastric juice were then determined.

Effect of Conquel on meal-stimulated secretion:—Eight patients with chronic duodenal ulcer were selected for this study. Each patient served as his own control, and two meal-stimulated gastric secretory studies were done in each patient on different days. A cross-over design was used, the odd-numbered patients were given 15 ml. of water in the first study, and two tablets of Conquel and 15 ml. of water in the second study. The even-numbered patients were given two tablets of Conquel and 15 ml. of water in the first study and 15 ml. of water in the second study.

The patient fasted for 14 hours and received no medicaments the day before the test. A nasogastric tube (No. 16F) was introduced orally or nasally under fluoroscopic observation so that its tip rested in the most dependent portion of the stomach. The patient remained in a sitting position and was instructed to expectorate all saliva. The stomach was emptied completely and a 4 ml. sample of gastric juice was obtained 15 minutes later. At this time the meal, consisting of 300 ml. of 10% peptone (Bacto-peptone, Difco Lab.), was given through the Levin tube by gravity. Four milliliter samples of gastric contents were then obtained at 15-minute intervals for 2½ hours. Fifteen milliliters of water as the control, or two tablets of Conquel and 15 ml. of water were ingested half an hour after the infusion of the meal. The pH, free (pH 3.5) and total (pH 7.0) acidities of each sample of gastric contents were then determined.

RESULTS

On basal gastric secretion:—Table I lists the effect of Conquel, Maalox liquid, Rolaids or Di-Gel on the free acidity and pH of the basal gastric secretion in 16 patients done at Station I. The statistical significance of differences between means of postantacid and basal values was determined by the students "t" test for unpaired comparison. A significant neutralization of the free acidities of the basal secretion was observed with each of the four antacids and it lasted for a 45-minute period. On the pH of the gastric secretion, Conquel produced a significant elevation of the pH which lasted for 90 minutes, while Maalox liquid, Rolaids and Di-Gel produced a significant elevation of the pH for 45 minutes only. The results on the effect of these antacids on total acidities were similar to those on free acidities.

TABLE II

EFFECT OF CONQUEL, MAALOX, ROLAIDS OR DI-GEL ON THE FREE ACIDITY AND pH OF THE BASAL GASTRIC SECRETION IN 16 PATIENTS AT STATION II

Type of antacid		Basal (minutes)				Postantacid (minutes)						
		15	30	45	60	10	20	30	45	60	75	90
Free acidity (mEq./l.)												
Conquel	mean	55	59	65	63	13*	13*	26*	43*	53	61	67
	S.D.	27.6	26.0	28.1	29	20.7	26.2	29.2	33.3	33.0	32.7	32.6
Maalox	mean	48	55	58	56	2*	12*	25*	26*	35*	45	50
	S.D.	25.1	26.7	25.6	27.5	2.8	23.4	37.0	34.2	36.8	37.0	40.0
Rolaids	mean	53	58	64	65	4*	6*	28*	41*	52	58	64
	S.D.	22.9	26.1	28.3	27.7	6.8	9.8	28.3	35.2	37.4	30.4	27.6
Di-Gel	mean	44	46	50	54	6*	8*	21*	32*	44	50	57
	S.D.	21.6	23.7	25.4	24.1	13.4	19.3	27.2	28.8	30.7	33.2	33.0
pH												
Conquel	mean	1.4	1.4	1.3	1.3	2.4*	2.7*	2.2*	1.6*	1.5	1.4	1.3
	S.D.	0.25	0.18	0.19	0.19	0.84	1.02	0.88	0.45	0.38	0.28	0.24
Maalox	mean	1.5	1.4	1.4	1.4	3.8*	3.3*	2.8*	2.6*	2.3*	2.9*	1.8*
	S.D.	0.26	0.23	0.23	0.24	1.30	1.60	1.61	1.52	1.46	1.38	1.23
Rolaids	mean	1.4	1.4	1.3	1.3	3.2*	3.0*	2.1*	1.8*	1.6*	1.4	1.3
	S.D.	0.21	0.21	0.17	0.18	0.94	0.91	0.92	0.72	0.55	0.24	0.19
Di-Gel	mean	1.5	1.5	1.4	1.4	3.4*	3.2*	2.4*	2.0*	1.7*	1.6	1.5
	S.D.	0.26	0.26	0.23	0.18	1.32	1.09	1.07	0.98	0.77	0.61	0.41

* $P < 0.05$ between the mean values of postantacid and basal periods.

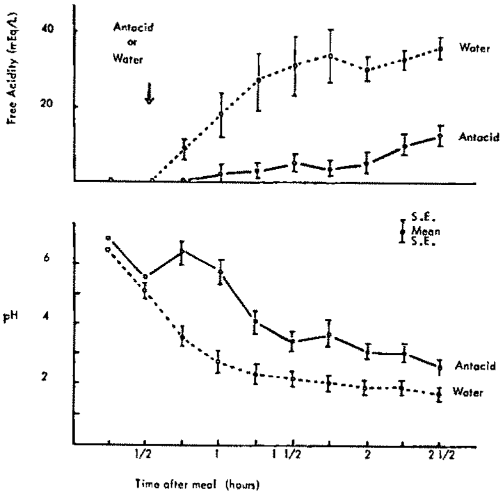

Fig. 1—Effect of water and antacid and water on meal-stimulated gastric secretion.

Table II lists the effect of Conquel, Maalox liquid, Rolaids, and Di-Gel on the free acidity and pH of the basal gastric secretion in 16 patients done at Station II. A significant neutralization of the free acidities of the basal gastric secretion was observed with each of the four antacids, for Conquel, Rolaids and Di-Gel, it lasted for 45 minutes and for Maalox liquid for 60 minutes. On the pH of the gastric secretion, Conquel produced a significant elevation of the pH values for 45 minutes, Rolaids and Di-Gel for 60 minutes and Maalox liquid for 90 minutes.

On meal-stimulated gastric secretion:—Figure 1 shows the mean and standard error of the free acidities and pH values of the gastric secretion after the ingestion of 300 ml. of 10% peptone and 30 minutes later, 15 ml. of water as the control or two tablets of Conquel and 15 ml. of water were ingested. Peptone meal acted as an acid neutralizer for the initial 30 minutes. After the ingestion of 15 ml. of water, both the free acidity and pH values of the gastric secretion rose to a level above the basal levels. After the ingestion of two tablets of Conquel and 15 ml. of water, however, a significant lowering of the free acidities and elevation of pH values of the gastric secretion was observed for a period of two hours, as compared with those after water only. Thus, Conquel, is a potent neutralizer of free acidity and raises the pH value of the meal-stimulated gastric secretion; the duration of action lasted for greater than two hours.

COMMENT

Conquel antacid is a low-compression tablet form which is softer and creamier than other antacid tablets. This is the result of a combination of sucrose, partially hydrogenated vegetable fat and a higher percentage of moisture. The active ingredient is micronized to provide a larger surface area upon dispersion. This combination of ingredients provided significant coating of the esophageal and gastric mucosa in man.[4] Because of its sodium and sucrose content, Conquel should be used cautiously in patients on a low-sodium or low sugar diet.

Our study of the comparative neutralizing effectiveness of four antacids on the acidity and pH of the basal gastric secretion in 32 patients showed that using the conventional doses of two tablets of Rolaids, two tablets of Di-Gel, 15 ml. of Maalox liquid, or two tablets of Conquel, they are equal in their acid neutralizing capacity. The duration of action lasted for 45-60 minutes. Conquel, in a dose of two tablets, was a potent buffer for the meal-stimulated secretion. The duration of action lasted for greater than two hours.

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Immunoglobulins in Submassive Hepatic Necrosis

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The presence of submassive hepatic necrosis in acute liver injury of viral or toxic etiology in liver biopsy specimens is of great diagnostic and prognostic significance. Liver biopsy, however, cannot be performed in some of these patients due to an abnormal coagulation profile. Hence, other noninvasive methods for diagnosis of submassive hepatic necrosis would be helpful. We compared the serum immunoglobulin-G levels in 15 patients with typical acute viral hepatitis and 19 patients with severe acute viral hepatitis with submassive hepatic necrosis. The difference of the Ig-G levels in both groups was statistically significant. By using discriminant analysis we found that it was possible to make the correct diagnosis of submassive hepatic necrosis in 89.5% of patients with acute viral hepatitis when only Ig-G levels were utilized.

Changes in serum gamma globulins occur in many acute and chronic liver diseases.[1-3] The association of high gamma globulin levels with hepatic cirrhosis is well known.[2] Increased serum Ig-G levels are most commonly seen in chronic active hepatitis and cryptogenic cirrhosis. Patients with alcoholic cirrhosis have additionally elevated Ig-A levels, while very high Ig-M levels are found in patients with primary biliary cirrhosis.

According to Popper and his associates,[4] there is proliferation of Kupffer cells and increase in lysosomal enzymes following liver cell damage with resulting increased immunoglubin synthesis.

In most patients with acute viral hepatitis, total globulin, gamma globulin, Ig-G and Ig-M levels are elevated during the first two weeks of illness. Giles and Krugman[5] reported a significant rise in the serum Ig-M levels beginning shortly after the onset of type A hepatitis, whereas these levels remained low or normal in type B hepatitis. Significantly lower Ig-M levels were found in type B hepatitis patients by Wollheim.[6] Kindmark and Laurell,[7] however, noted increased Ig-M levels in patients with type B hepatitis. Vittal and associates[8] did not find statistically significant differences in the degree of elevation of serum Ig-M levels between patients with HBsAg-negative and HBsAg-positive acute viral hepatitis. A majority of patients with type A and type B acute viral hepatitis showed mild elevation in total globulin, gamma globulin and Ig-G levels[5, 6, 8, 9] during the first two weeks of the illness. These values became completely normal by the 12th week. No prognostic significance was found between the course of the disease

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TABLE I

Patient	Age	Sex	HBAg	SGPT	Globulin	γ Globluin	Ig-G	Ig-A	Ig-M
MG 1	25	M	+	992	2.8	1.32	1,365	164	196
FS 2	36	M	+	452	3.9	1.92	1,880	670	270
LB 3	26	M	–	1,340	2.5	1.10	1,010	143	67
JH 4	25	M	+	800	3.6	1.60	1,690	298	283
WJ 5	42	F	+	460	4.0	2.00	1,975	687	204
MT 6	24	M	+	1,127	4.0	1.72	1,575	222	227
OP 7	21	M	+	1,655	4.3	2.24	1,840	163	353
DK 8	19	M	+	1,712	3.7	1.96	1,735	312	229
DW 9	19	F	–	381	3.7	1.55	1,360	470	197
HP 10	44	M	–	372	3.6	1.55	1,485	219	242
TJ 11	30	M	–	940	4.2	2.67	1,810	397	471
IT 12	34	M	+	1,659	3.8	2.00	1,815	322	670
PD 13	21	M	+	1,331	2.7	1.44	1,210	73	176
PL 14	17	M	+	1,409	3.0	1.58	1,325	175	375
SR 15	19	M	+	247	4.2	2.80	2,450	202	520

Patients with classical acute viral hepatitis.

and the changes in the immunoglobulin levels.

As far as we know there is no study on immunoglobulins in patients with submassive hepatic necrosis secondary to acute viral hepatitis. Diagnostic or prognostic significance of the changes in the immunoglobulin levels in submassive hepatic necrosis have apparently not been reported. Because of this, we determined the immunoglobulin levels, particularly the Ig-G, in every patient with acute viral hepatitis, so as to find out whether the levels of immunoglobulins can be of prognostic and/or diagnostic significance. At the same time, other parameters such as serum total globulins, serum gamma globulins, HBsAg and enzymes were determined.

Material and Methods

Thirty-four patients with acute viral hepatitis were included in the study. The diagnosis was established in each case on clinical, biochemical and liver biopsy findings within four weeks after the onset of symptoms. Most of the patients had an

TABLE II

Patient	Age	Sex	HBsAg	SGPT	Globulin	γ Globulin	Ig-G	Ig-A	Ig-M
JN 1	31	F	–	1,650	3.9	1.80	700	350	95
TL 2	25	M	+	452	3.7	1.80	1,275	480	340
DG 3	22	M	+	356	4.3	2.45	1,475	176	420
RS 4	27	M	+	1,095	3.3	1.00	810	100	26
SM 5	17	F	+	1,088	3.8	1.70	1,130	208	150
AS 6	29	M	+	252	3.6	2.00	1,360	125	590
CB 7	21	M	+	3,760	3.9	1.50	1,150	125	105
CB 8	36	F	+	1,640	2.5	2.20	1,800	340	310
JB 9	21	F	+	4,000	3.7	1.60	820	255	480
GB 10	25	F	+	1,440	2.3	1.20	540	160	530
DC 11	35	F	+	3,060	3.7	1.20	710	210	210
JB 12	32	F	–	1,610	1.5	1.20	760	210	210
JT 13	24	M	+	1,580	2.4	1.38	1,310	163	410
EH 14	17	M	+	408	4.0	1.80	1,385	90	465
CB 15	21	M	+	651	2.6	1.23	1,085	274	75
AB 16	24	F	–	758	3.4	1.80	925	262	342
RC 17	54	F	+	294	2.6	1.70	1,080	274	144
OL 18	19	M	–	2,274	3.0	1.92	1,650	340	217
AH 19	30	M	–	670	2.8	1.02	870	127	181

Patients with submassive hepatic necrosis.

abnormal coagulation profile and therefore fresh frozen plasma transfusion had to be given to them before a liver biopsy could be performed. (The immunoglobulin levels were determined before the plasma transfusions were given).

Fifteen patients who revealed the classical features of acute viral hepatitis on biopsy without evidence of submassive or massive liver cell necrosis were used as controls. These 15 patients were randomly chosen from a group of 300 patients with acute viral hepatitis who were admitted to the hospital during the last two years. The other 19 patients were cases of total submassive hepatic necrosis diagnosed during the same period of time by liver biopsy which exhibited the features of submassive hepatic necrosis with intralobular and interlobular zones of hepatic necrosis and collapse that bridged adjacent portal triads or central veins, or both, as previously described by Boyer and Klatskin.[10]

On admission, blood samples were tested for HBsAg, total globulin, gamma globulin, Ig-G, Ig-A, Ig-M and enzymes from each patient. HBsAg was tested by solid phase radioimmunoassay (Ausria 125, Abbott Laboratories, North Chicago, IL). Globulin and gamma globulin determinations were done by electrophoresis. Quantitative immunoglobulin estimation was performed by radial immunodiffusion. The results are shown in Tables I and II.

RESULTS

Classical acute viral hepatitis (15 patients): Seventy-three per cent of the 15 patients with biopsy findings of classical acute viral hepatitis had a slight elevation of globulins (mean: 3.6 gm./100 ml.). The gamma globulins were slightly elevated in all patients except one. (mean: 1.83 gm./100 ml.). Ig-G (N = 900-1,300) was elevated above normal in 13 and within normal limits in the other two patients with a mean of 1,635 mg./100 ml. No levels below normal were found. Elevation of the Ig-M (N = 60-145) was present in 14 patients (mean: 305 mg./100 ml.)

Submassive hepatic necrosis (19 patients): Forty-seven per cent of the 19 patients who had submassive hepatic necrosis on biopsy findings showed lower levels of serum globulins (mean: 3.21 gm./100 ml.). Thirteen of 19 patients had increase in values of gamma globulins (mean: 1.60 gm./100 ml.).

The Ig-G levels were below normal ranges in seven patients, within normal ranges in six and slightly elevated in six. Among the latter six patients, three showed only very slight elevations (e.g. 1,300, 1,360, and 1,385) above the normal ranges. The Ig-M levels were moderately elevated in 14 patients (mean: 279 mg./100 ml.).

COMMENT

Both types of lesions (acute viral hepatitis and submassive hepatic necrosis) were encountered in patients of all ages (range: 17-54 years) (Table III). Although most of the patients with submassive hepatic necrosis were over 40 years of age in a previous report,[10] the age group in the two groups we studied were almost alike. Females comprised almost 50% of all cases with submassive hepatic necrosis, while males predominated in the acute viral hepatitis group. The sex distribution of our patients appears different from that in Boyer and Klatskin's patients who did not have a significant sex difference.

In confirmation of previous reports, our patients with classical viral hepatitis showed definite elevation of total globulin, gamma globulin, Ig-G and Ig-M levels in the initial four weeks of the illness. In the patients with submassive hepatic necrosis, however, the serum globulins and gamma globulin values were only slightly elevated.

The difference between the Ig-G levels in the two groups was statistically significant ($P < 0.01$). Only six of the 19 patients with submassive hepatic necrosis (31.55%) showed slight elevations of the Ig-G level above normal ranges, while 86% of patients with classical viral hepatitis had elevated Ig-G levels. Seven patients with submassive hepatic necrosis comprising nearly 37% of patients in the same group had low Ig-G levels. One of these

TABLE III

CUMULATIVE AND MEAN VALUES IN THE TWO CATEGORIES OF PATIENTS

	Acute viral hepatitis	Submassive hepatic necrosis
Age	26.8	26.8
Sex		
Female	2	9
Male	13	10
HBsAg		
Positve	11	14
Negative	4	5
Enzyme (SGPT)	992	1,423
Globulin	3.6	3.21
γ globulin	1.83	1.60
Ig-G	1,635	1,097
Ig-A	302	225
Ig-M	305	279

patients died after a fulminant course. One patient who had normal Ig-G level with submassive necrosis also died after a similar fulminant course. Another patient whose Ig-G level was minimally elevated (1,310 mg./100 ml.) died in the second week of his illness. No death was observed in the classical acute viral hepatitis group of patients or in patients with submassive hepatic necrosis who had significantly elevated Ig-G levels.

By using discriminant analysis* we found that it was possible to make the correct diagnosis in 89.5% of patients with submassive hepatic necrosis and in 93.3% of patients with acute viral hepatitis when both groups were matched for Ig-G levels.

Thus, it appears that in the first four weeks of illness, the increase of the gamma globulin levels in acute viral hepatitis is a result of the increase in synthesis of Ig-G and Ig-M, while elevation in submassive hepatic necrosis is a result of the increase in the Ig-M levels alone.

It is difficult to explain the normal or low levels of Ig-G in patients with submassive hepatic necrosis. We have serial immunoglobulin determinations in seven patients of submassive hepatic necrosis who had low Ig-G levels during the acute phase of the disease. Follow-up of these patients up to eight months showed no increase in Ig-G levels. Initial low levels of Ig-G persisted during this period. It is well known that patients with agammaglobulinemia and severe combined immunodeficiency have increased susceptibility to hepatitis virus and infection with this virus may lead to a progressively active or fulminating form of hepatitis resulting in death.[11] Perhaps the patients with subnormal or low Ig-G levels are more prone to develop severe necrosis when infected with hepatitis virus. It is difficult to reach a conclusion in this regard with a small group of patients. Therefore we accept that the normal or low levels of Ig-G in patients with submassive necrosis is still problematic at present and should be checked in the future in a larger series of cases. Furthermore, the over all immune competence of these individuals was not tested.

The definitive diagnosis of massive or submassive hepatic necrosis is often difficult in patients with acute hepatitis when a liver biopsy cannot be obtained because of abnormalities in their coagulation profile which contraindicates a blind punch biopsy. In such patients the findings of decreased or normal Ig-G levels may suggest the presence of severe hepatocellular damage with possible massive or submassive necrosis. Despite the fact that two patients with low and one patient with minimally increased Ig-G levels died, it may be difficult to ascribe prognostic significance to low Ig-G levels in patients with severe acute viral hepatitis. Serial estimations of Ig-G levels in larger numbers of patients may be needed to determine whether Ig-G levels remain low in patients with fulminant hepatitis throughout the course of the disease and their influence on the outcome.

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Communication from Abroad

The Value of Emergency Angiography in the Diagnosis and Prognosis of Acute Mesenteric Arterial Insufficiency

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Selective angiography is the technic which provides a higher accuracy in diagnosing an acute mesenteric arterial insufficiency. If carried out at an early stage it surpasses any other technic. It permits not only obtaining topographic data to locate the occlusion but also the detection of aspects of the collateral circulation in the loops of the bowel, thus enabling us to determine the therapeutic procedure to follow.

We have done selective angiography of the superior mesenteric artery in nine patients in all of whom we identified the embolic disease. In five of these patients the embolus was in the main trunk and in four it was in the distal branches. The mortality rate varied depending on the site of the embolus and the time elapsed in the process. In three of the patients with distal localization and in one with trunk localization and sufficient arterial permeation, a conservative therapy was used with good results in all of them.

INTRODUCTION

The high mortality rate resulting from acute mesenteric arterial insufficiency, occurs, according to most authors, from a late diagnosis,[1-4] partly because the initial clinical signs, laboratory methods and conventional roentgen examinations are usually not conclusive.[5, 6] Most often, these circumstances lead to a laparotomy after a long period of observation following the onset of the arterial occlusion. This explains the discouraging results obtained after massive intestinal resection, with a mortality rate sometimes greater than 90%.[7]

Among the most common causes of acute bowel ischemia are the occlusive ones caused by emboli and thrombosis and the nonocclusive or reversible ones which occasionally accompany such clinical conditions as congestive heart failure, hemorrhagic shock and the hemoconcentration.[8] Aakhus,[9] was the first to consider the selective mesenteric angiography as the ideal method for studying these patients. It is advisable to perform it at the earliest pos-

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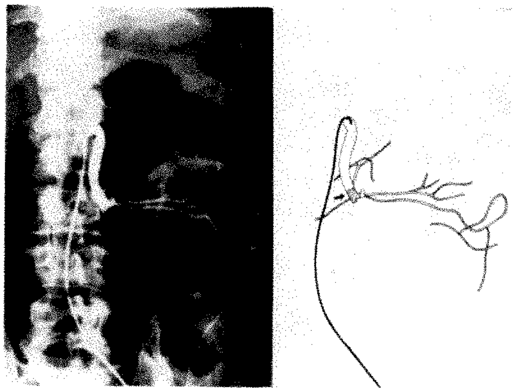

Fig. 1—Acute embolic occlusion of the superior mesenteric artery. Absence of distal permeation.

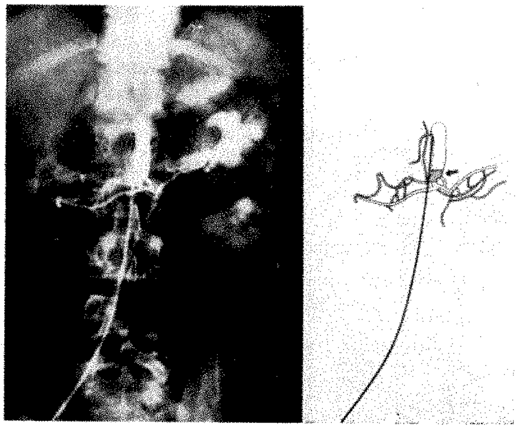

Fig. 2—Acute embolic occlusion of the superior mesenteric artery.

sible stage technically feasible consistent with the patient's general condition.

Material and Methods

During the last six years we have seen 32 patients with acute mesenteric arterial insufficiency. In 29 of them laparotomy was performed, carrying out a massive bowel resection in 21, a limited resection in seven and an embolectomy in one. The mortality rate was 75%.

It was possible to perform selective angiography in nine patients by the fifth day from the onset of the clinical picture. In these patients the ECG detected atrial

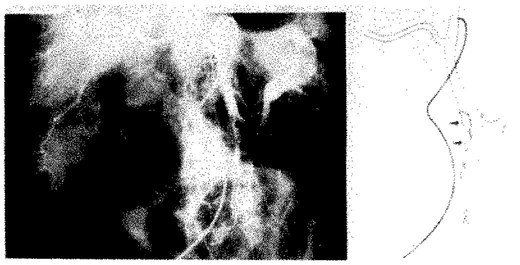

Fig. 3—Acute embolic occlusion of the superior mesenteric artery with insufficient distal permeation.

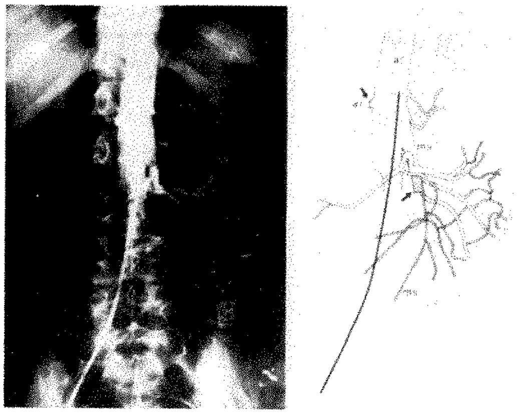

Fig. 4—Aortography. Aorta (a) acute complete occlusion of the superior mesenteric artery, (ms) with sufficient distal permeation. Simultaneous acute occlusion of the right renal artery (ar).

fibrillation, which was caused by a left-sided valvular disease in eight and by a miocardiopathy in one. The patients' ages ranged from 30-60 years. In four of these patients there was ischemic history in other zones and a femoral embolectomy had previously been done in two. None of the patients had shown prior symptoms of acute intestinal ischemia. Angiography was performed one to five days following the onset of symptoms, usually within a few hours after admission.

Percutaneous transfemoral aortography,[10] in the anteroposterior and lateral positions, was initially done using 30 ml. of Urografin 60%. The lateral position is essential to visualize the first segment of

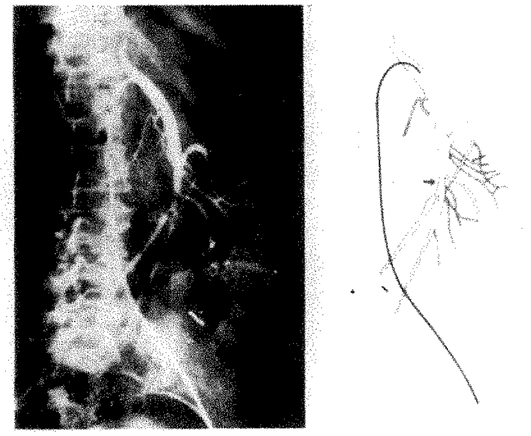

Fig. 5—Follow-up angiography of the superior mesenteric artery of previous case (Fig. 4), six months after occlusion. A total permeation of the artery is observed.

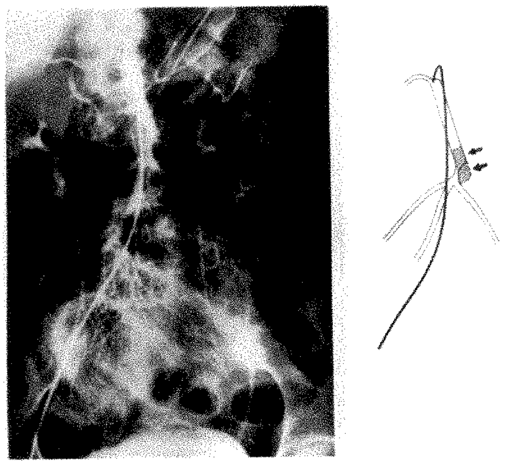

Fig. 6—Embolus in the superior mesenteric artery.

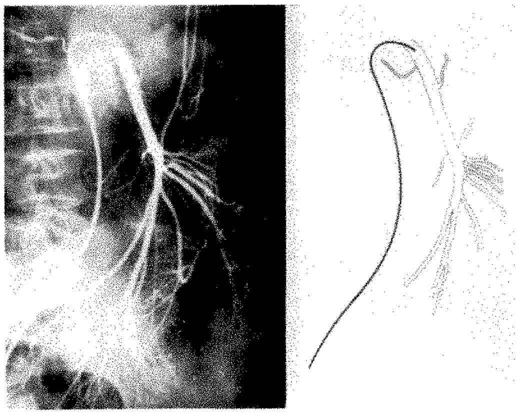

Fig. 7—A new angiographic study of the previous case was performed two weeks after embolectomy, with total permeation of the main trunk.

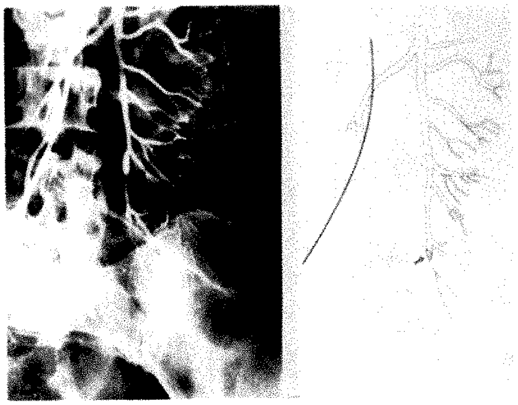

Fig. 8—Distal embolus at ileocolic artery level.

the superior mesenteric artery, since it is always obscured in the frontal projection and usually by-passed during a selective study.

Selective angiography was performed for a more detailed study of the superior mesenteric arterial tree using 10-20 ml. Urografin 45%.

Results

The clinical picture resembled an acute abdominal disease and in four cases was accompanied by bloody stools. A leucocytosis of between 12,000 and 26,000/cu. mm. was confirmed in all patients. All plain abdominal films showed suggestive signs of intestinal ischemia, although not always conclusively. In the cases in which selective angiography of the superior mesenteric artery was done, embolic disease could be identified as being responsible for the acute abdominal disease.

The angiographic findings, evaluated in order to determine therapeutic procedure were: 1. embolus localization either in the main trunk of the mesenteric superior artery or in the distal branches; 2. the existence of multiple emboli in collateral channels; 3. the presence of emboli in

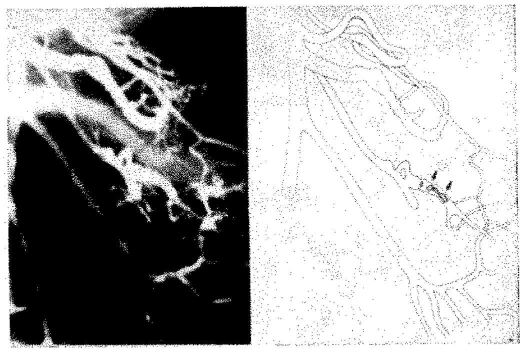

Fig. 9—Detail of distal embolism jejunal branches with good collateral circulation.

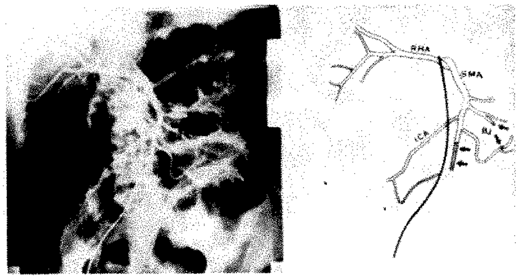

Fig. 10—Multiple emboli in jejunal branches (BJ). Right hepatic artery (RHA). Superior mesenteric artery (SMA). Ileocolic artery (ICA).

other abdominal arteries; 4. the evaluation of the supplementary collateral circulation at the level of the loops of ischemic bowel and finally, 5. the possible distal permeation of the artery from the embolus in late stages.

In five cases, the embolus lay in the main trunk of the superior mesenteric artery at a greater distance than 4 cm. from its origin; the collateral circulation and the distal permeation were nonexistent in three of these cases. It was therefore decided to do a laparotomy.

In two of the latter three cases (Figs. 1 and 2) the selective angiography was performed four and five days respectively after the onset of the clinical picture. At laparotomy an extensive intestinal necrosis was observed, which forced a massive intestinal resection. In the third case (Fig. 3) the angiography was performed prior to the elapse of 36 hours, revealing an insufficient arterial blood flow. For this reason an embolectomy was performed first but as it did not restore the blood flow in the superior mesenteric artery and the intestinal mucosa did not recover its pinky red color, it was necessary to bring about a massive resection as in previous cases. These patients died following a very troublesome postoperative period.

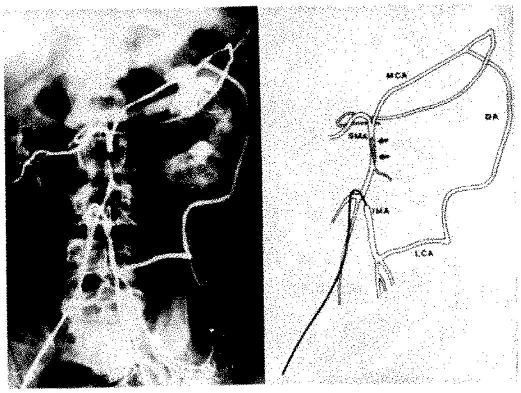

Fig. 11—Anastomosis of left colic artery (LCA) branch of inferior mesenteric artery (IMA) with middle colic artery (MCA) branch of superior mesenteric artery (SMA) and forming the so-called marginal or Drummond's artery (DA). A second embolus even more distal in the superior mesenteric artery is observed. Right hepatic artery (RHA).

An early angiography was performed in the fourth patient (Fig. 4) before 12 hours elapsed and an apparently sufficient arterial blood flow from the embolus and a good collateral blood circulation at level of the affected loops of the bowel was seen. For this reason, an intensive anticoagulant therapy with heparin (50 mg./3 hr.) and spasmolytic agents were immediately used with satisfactory results. A new angiographic study six months later (Fig. 5) showed a total permeation of the superior mesenteric artery trunk. The only sequel was a discrete arterial stenosis that did not cause, at any time, symptoms of chronic intestinal ischemia. In the first examination (Fig 4).

of this case, the aortography showed the existence of another embolus in the right renal artery, which did not cause signs of acute renal insufficiency.

As in the previous case, in the fifth patient the angiography was performed at an early stage and a good collateral blood circulation at the level of the affected loops of the bowel was also observed (Fig. 6). Nevertheless, the presence of a big embolus required an embolectomy, thus obtaining a complete permeation of the artery, followed by a satisfactory course. Follow-up angiographic study performed two weeks later (Fig. 7), showed a total permeation of the main trunk.

In the remaining four patients, the localization of the emboli was distal; in one case in the ileocolic artery (Fig. 8) and in the other three the emboli were multiple in the jejunal branches (Figs. 9 and 10). After having observed a good collateral circulation at the loops of the bowel level in the three cases intensive anticoagulation therapy with heparin (50 mg./3 hr.) and spasmolytic agents were immediately started with a satisfactory result in all of them. In the fourth case, the diagnosis was delayed and a limited resection had to be done with a satisfactory final result.

In one of the cases with occlusion in the main trunk of the superior mesenteric artery, the distal arterial tract from the embolus could be demonstrated from the so-called marginal or Drummond's artery, by catheterization of the inferior mesenteric artery. A second embolus, even more distal in the superior mesenteric artery (Fig. 11), was also seen.

COMMENT

The superior mesenteric artery embolism is the most frequently described cause of acute mesenteric arterial insufficiency,[11-13] its incidence being higher than the inferior mesenteric artery embolism because: 1. the superior mesenteric artery is wider than the inferior artery; 2. the origin of the inferior mesenteric artery is further distal in the aorta than that of the superior mesenteric artery and the inferior mesenteric artery originates in the aorta at a wider angle than the superior artery, which runs almost parallel to it.[14]

Usually, the clinical picture of the occlusion in the main trunk is similar to that of the occlusion in the distal branches although of greater intensity[15] and it occasionally presents an insidious onset which makes early diagnosis difficult, thus increasing the already high mortality rate. Generally speaking, an acute mesenteric ischemia should be suspected in a patient with atrial fibrillation, severe abdominal pain, anamnestic data of previous embolism and bloody stools.[16] From the biochemical point of view there is no parameter worthy of interest, leucocytosis being the earliest to appear.[17] Acute mesenteric arterial insufficiency may be suspected, although never in a conclusive way, by a plain abdominal film, upper gastrointestinal series and barium enema studies. The roentgen findings are always difficult to evaluate and in any case they do not indicate the intestinal damage which can vary from edema to complete intestinal necrosis and gangrene.[18]

This high mortality rate increases because most of the cases are not diagnosed in their early stages and also because the disorder usually affects old persons with serious complicating diseases (mainly heart disorders) who require digitalis. This increases the widespread arterial spasm associated with occlusive disease.[19]

Selective angiography surpasses any other technic in providing a more accurate diagnosis. Following this technic, topographic data of great interest can be obtained. The existence or nonexistence of a distal permeation from the embolus, the arterial blood flow of the damaged bowel wall as well as a possible anastomosis with other branches, can be evaluated; thus determining the therapeutic pattern. Previous aortography in the anteroposterior and lateral positions, must always be performed to allow visualization of the first segment of the superior mesenteric artery and to detect the presence of emboli in other abdominal arteries.

Occasionally, when the emboli are very small and are localized in the finer arterial branches, the angiography may not show the occlusion. The only demonstrable angiographic findings may be the generalized and marked narrowing of the superior mesenteric arterial tree, associated with reduced blood flow, which occurs either as a consequence of an increased sympathetic tone as a defense mechanism against the shock,[5] or through a discharge from the clot of vasoconstrictor substances.[20]

With reference to the therapy, if the angiography shows an embolus in the main trunk without distal permeation and there has been an early diagnosis, an embolectomy should be attempted, since this surgical technic reduces the mortality rate by up to 50%[15, 21] This allows us, at the same time, to effect a sympathectomy and the intra-arterial administration of spasmolytic agents which help to overcome the widespread vascular spasm which impairs the prognosis. Occasionally, in spite of the total intestinal recovery after embolectomy, an intestinal stenosis may appear in a later stage, generally after two or three months, that may even require intestinal resection.

If diagnosis is delayed for over 24-48 hours and on carrying out laparotomy the loops of the bowel appear to be necrotic, a resection the extent of which will depend on the amount of the damage, will become unavoidable. This resection will be carried out always on healthy and well vascularized tissue. In such circumstances the mortality rate is very high, mainly when the embolus lies in the main trunk of the superior mesenteric artery, as happened in three cases in our series.

When the angiography shows sufficient distal permeation in the cases of emboli in the main trunk or a good collateral circulation at the level of the affected loops of the bowel in the cases of distal emboli, it is advisable to adopt a conservative treatment with spasmolytic agents and intensive anticoagulant therapy which gives the highest percentage of survival. In four cases in our series the survival rate was 100%.

Concluding, we suggest the great importance of carrying out the mesenteric angiography as early as possible in any patient suspected of an acute mesenteric ischemia, since the therapy to be adopted and the prognosis will depend on the angiographic findings.

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Meconium Ileus Equivalent

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A case of meconium ileus equivalent in a 30-year old man is presented. The pathology and therapy for the condition are discussed.

Mechanical intestinal obstruction associated with mucoviscidosis of the new-born is well known. A less well known complication of cystic fibrosis in older patients, meconium ileus equivalent, will herein be discussed.

CASE REPORT

R. K. was admitted to the St. Vincent's Hospital, Montclair, NJ, on 12 March 1973 because of abdominal distention, vomiting and obstipation of several days. He had suffered with cystic fibrosis since infancy and had been hospitalized several times for pulmonary problems, his most recent admission being 13 January 1973. A similar episode of abdominal pain was treated by his own physician at home one year earlier.

Examination on admission revealed a very ill 30-year old man who had a markedly distended abdomen. Blood pressure, 100/80; temperature, 38° C; respiration, 30. The patient experienced some distress breathing. CBC and electrolytes were normal except for a CI of 91. X-ray (Fig. 1) revealed dilation of small bowel with gas, with minimal gas in the large intestine. The film was consistent with a diagnosis of small bowel obstruction. Chest x-ray revealed diffuse infiltration in both lung fields with interstitial fibrosis consistent with the diagnosis of cystic fibrosis (Fig. 2).

Management included intravenous fluids and inhalation therapy and an antihistamine drug. The next day the patient's abdomen continued to be distended. A tap water enema was given without success. A Cantor tube was inserted and attached to suction.

An enema was given on 14 March with gastrografin but was not effective. Defects were seen in the distal small bowel and ileum, probably representing impacted stool believed the cause of the obstruction (Fig. 3).

The abdomen was more tender now and the bowel sounds quieter. The patient was taken to surgery. Surgical findings included marked dilation of the small bowel and fluid in the abdomen. The distal small bowel and appendix were filled with impacted material which caused that portion of bowel to lie low in the lower abdomen on the right. An enterostomy was done at the point of maximum inspissation and tenacious meconium-like stool removed manually. Irrigation of the area with N-acetylcysteine was done with benefit. The appendix was removed and a Foley catheter placed into the bowel by way of the stump of the appendix. The catheter was to be used for irrigation of the area with N-acetylcysteine in the future, if needed. The enterostomy wound was closed. The Foley catheter was brought out via a stab wound. A Penrose drain was placed in

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From the Departments of Surgery and Medicine, St. Vincent's Hospital, Montclair.

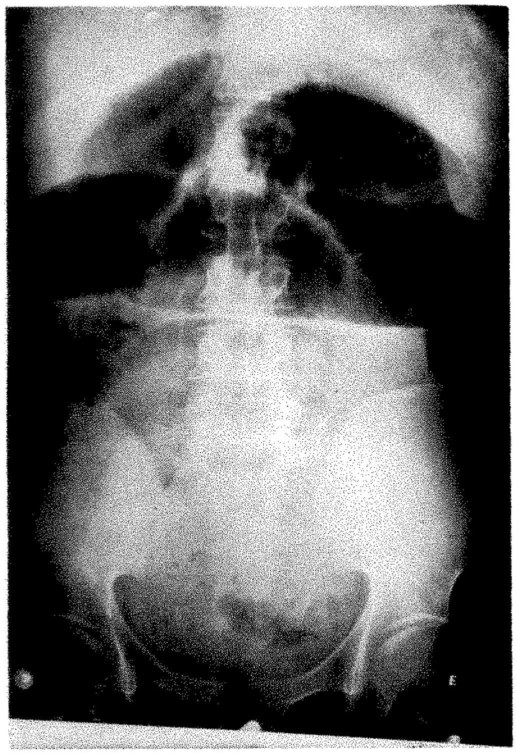

Fig. 1—Dilation of small bowel with gas and minimal gas in large bowel is present. The findings are consistent with small bowel obstruction.

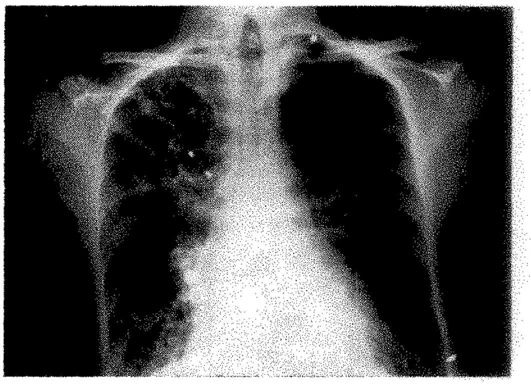

Fig. 2—Infiltrates in both lung fields with interstitial fibrosis consistent with cystic fibrosis are present.

the pelvis and right colic gutter. The patient tolerated the procedure fairly well.

The patient slowly improved following surgery. His main problem was pulmonary. He was now also attended by a pulmonary specialist who advised an endotracheal tube and ventilatory assistance. This was begun on 14 March. In addition, Solucortef,® ampicillin and Garramycin® and intravenous fluids were administered. On 17 March, the patient moved his bowels via the rectum.

He continued to have respiratory problems, as evidenced by abnormal arterial blood gas values, in spite of ventilatory support. On 18 March, however, the arterial blood gas values were normal. He was transfused for his anemia. On 20 March, in spite of specialized pulmonary care, the x-rays revealed a slight increase in lung infiltration.

Attempts were made to wean the patient from the respirator but were unsuccessful. The endotracheal tube became more difficult to manage having been in place for seven days. A tracheostomy was advised by the pulmonary consultant and was performed on 22 March. The patient had cardiac arrest in the operating room, following the procedure. He responded favorably to electric shock. He was transferred to intensive care where he again arrested and died on 22 March in spite of cardiopulmonary resuscitation.

Laboratory data:—Electrolytes were well maintained throughout. Pulmonary problems were always present and CO_2 was elevated frequently. Cultures of tracheal secretions revealed *proteus vulgaris.* The sputum contained pseudomonas, sensitive to ampicillin, Geopen® and clindamycin. The day of death, the patient had a hemoglobin of 10.2 gm. and a WBC of 6,700 with a normal differential.

The autopsy revealed no point of obstruction of the intestine with some fibrinous adhesions between the small bowel loops in the right lower quadrant, the area of cecostomy. Histologic changes of cystic

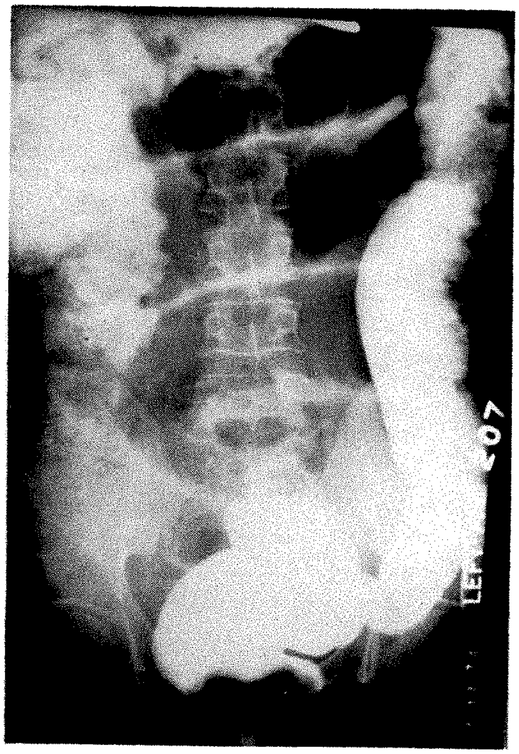

Fig. 3—Defects are present in the distal small bowel, probably representing impacted stool believed the cause of the obstruction.

fibrosis were present in the lungs, pancreas and liver.

COMMENT

Cystic fibrosis, also known as fibrocystic disease of the pancreas, is a well defined inherited clinical entity, associated with deficiency or absence of pancreatic intestinal enzymes, abnormal intestinal mucoprotein in the small intestine, increased viscidity of the endobronchial secretions and elevated serum chloride in the sweat. The disease involves the exocrine glands. Meconium ileus intestinal obstruction occurs in about 10% of the neonates with this disease. Abnormal mucous glands secrete thick viscid mucous and salivary glands which, although normal histologically, secrete abnormal amounts of sodium chloride.[1] Cystic fibrosis, the most common clinical malabsorption state, pertains to malabsorption of fat at the time of hydrolysis by pancreatic enzymes.[2]

Landsteiner first reported meconium ileus in 1905 in an autopsy report of an infant. Blackfan and Wolbach in 1933 noted that the pathological process in the pancreas appeared to be inspissation of the secretions. Cystic fibrosis was described as a clinical entity and named by Franconi, et al in 1936. All were cited by Hunton, Long and Tsumagari.[1]

Jensen, in 1962, named the disease while reporting the case of a 15-year old boy having mucoviscidosis and intestinal obstruction.[3]

A survey of the literature suggests about 40 cases of meconium ileus equivalent ranging from two to 31 years.

Etiology:—It was originally thought that meconium ileus was caused by a lack of pancreatic enzymes producing inadequate digestion of intestinal contents. The same phenomenon was believed pertinent to meconium ileus equivalent.

Glanzman suggested that meconium ileus was due to abnormal mucus secretions, not pancreatic insufficiency. Bodain thought that enzyme lack was contributory but abnormal intestinal mucus was the primary cause. Hunton, Long and Tsumagari[1] also refer to the above named authors.

DiSant'Agnese and associates, quoted in reference 1, have shown that the mucus is abnormal. Its water solubility is altered and unaffected by trypsin. Jensen thinks the material originates in the intestinal goblet cells.[3]

Clinical data suggesting meconium ileus equivalent include intestinal obstruction in a patient suspected of having fibrocystic disease, pain and tenderness over

McBurney's point, soft palpable mass in the right lower abdomen and plain abdominal x-rays showing bubbly material (Newhouse's sign).[1]

The number of adults with fibrocystic disease will grow due to increasing knowledge of the illness and better supportive measures available for children. DiSant'-Agnese and Anderson feel the problems will be more pulmonary and the gastrointestinal complaints will be less.[4] This has been true. One, however, must be aware of the adult complication, meconium ileus equivalent, as in this case. Cystic fibrosis in the adult may be further confirmed by selenomethione scanning of the pancreas. The diseased pancreas fails to take up 75 Se-labeled selenomethionine.[5]

The initial approach to treatment for patients with meconium ileus equivalent should be nonoperative. Attempts to relieve the obstruction include the use of the long intestinal tube, hydration and possible use of mucolytic agents by way of the long tube and rectal enemas.[6]

An enema using Gastrografin, which will create a hyperosmolar state in the intestine thus drawing fluid into the intestine to assist in moving the meconium along, may be of value. The importance of free flowing intravenous balanced electrolyte fluid support when Gastrografin is used as an enema is obvious.[7]

Therapy for meconium ileus has also included surgery to remove the tenacious material in the bowel and the formation of an enterotomy. Some success has been achieved with enemata to cause passage of the thick material. Resection of the area of maximum inspissation causing obstruction has also been done.

The importance of pancreatic secretion needs clarification for patients who have responded favorably to treatment with enzyme replacement. It may be that the intestinal wall producing the abnormal mucous and the pancreas features producing the enzymes are both important.

N-acetylcysteine acts by breaking disulphide bonds in the mucoprotein molecule. In 4% concentration it is slightly hyperosmolar and thus draws fluids from the intestinal wall. These two properties explain its usefulness in the case of intestinal obstruction due to meconium ileus.[8]

In this case following no relief of the obstruction after seven days, surgery was in order. At surgery, one will usually find, as in this case, putty-like material occluding the terminal intestine, appendix, cecum and sometimes right colon. Removal of the material via enteric stomata may be effective. Resection of the area containing the inspissated material may be needed.[6] The inspissated material may act as a lead point for an intussusception.[9]

Therapy has also included use of a Fogarty catheter to help release the inspissated material.[10]

N-acetylcysteine has been used prophylactically by mouth to prevent meconium ileus equivalent. It has been used in patients having fibrocystic disease who are getting older.[11]

SUMMARY

A case of meconium ileus equivalent in a 30-year old man has been presented. The etiology, pathology and therapy for the condition has been discussed.

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Intestinal By-pass in the Treatment of Morbid Obesity*

A REPORT OF 120 SUCCESSIVE CASES WITHOUT MORTALITY

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Morbid obesity is defined as adiposity sufficient to cause socioeconomic, reproductive or life-threatening disability in otherwise normal persons.[1] Obesity, a product of an affluent society, has reached epidemic proportions in the United States[2] and is not only a disease in itself but a perpetrator of others.[3] Due to many associated conditions, the mortality of obesity rises in proportion to its extent. Althought this entity has been investigated thoroughly and the associated morbidity has been well demonstrated, the cause of morbid obesity remains obscure. The lack of an effective treatment persists. Diet, drugs and psychiatric therapy have had little lasting influence on the food addict.

METHOD

Beginning in 1970, our first 30 cases were treated by anastomosing the proximal jejunum transected 30 cm. from the ligament of Treitz, end-to-end to the distal ileum transected 15 cm. above the ileocecal valve. The proximal end of the nonfunctioning intestine was closed and anchored to the transverse mesocolon and its distal end was drained into the cecum.

In the subsequent 90 patients we modified our first procedure by increasing the length of the proximal jejunum to 35 cm. and distal ileum to 20 cm. The nonfunctioning intestine was closed proximally and drained distally into the cecum, as was described previously.

MATERIAL

In the selection of patients we have followed the criteria of Scott, et al,[4] Payne, et al[5] and others: double or triple ideal body weight of at least five years' duration with failure of medical and dietetic treatment, absence of correctable endocrinopathy, absence of any medical condition which precludes surgery, age below 50 years, presence of certain complications (Pickwickian syndrome, diabetes mellitus of adult onset, hypertension), adequate intellect and emotional reserve. One hundred and twenty obese patients underwent the intestinal by-pass since 1970; 83 were female and 37 male. Their ages ranged from 14-42 years. The greatest number of them were between 22 and 32 years of age (Fig. 1). All were white with the exception of one negro male. Their weights varied from 112.5-213.75 kg. and their heights from 15.5-18.25 m. (Fig. 2).

All of these individuals had previously received some kind of intensive medical, dietetic and psychiatric treatment; some of them for over several years, with negative results. Thirty patients had elevation of fasting blood sugar and abnormal glucose tolerance tests and were treated as diabetics. Twenty-eight of them had hypertension. Twelve patients had fatty meta-

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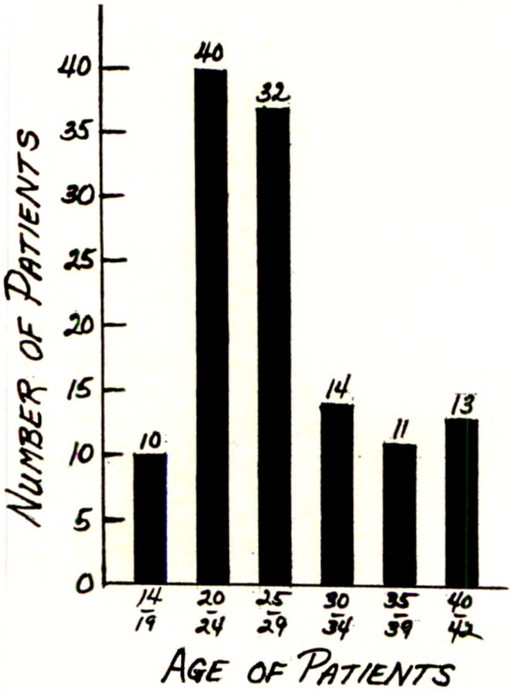

Fig. 1

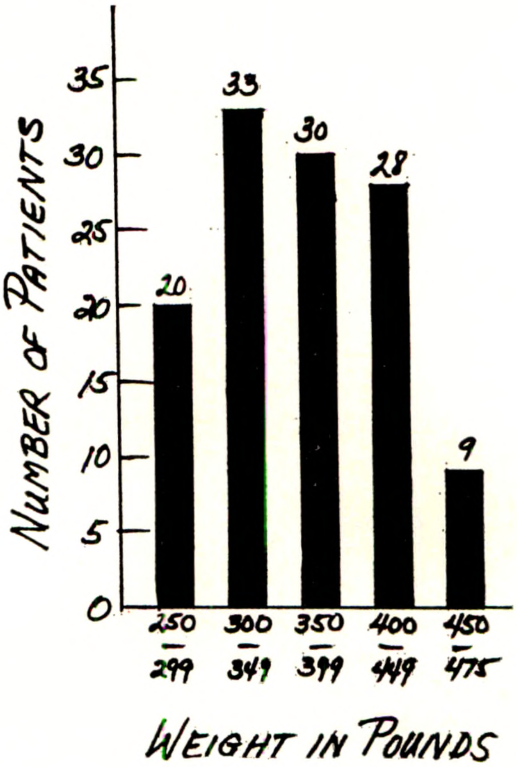

Fig. 2

morphosis of the liver as shown by liver biopsy at time of surgery.

RESULTS

Out of the first group of 30 patients (Table 1), 20 had troublesome diarrhea, some requiring Lomotil® daily for up to six months. Two of them had three to four liquid stools per day for over four years. Seven individuals complained of constant and great abdominal distention for three to four years following surgery. Two in this group lost weight below ideal levels and were placed on a high protein diet with good result. The original group of 30 patients lost an average of 58.55 kg. during the first year and 22.5 kg. the second year. The great majority of them came to a stable weight in a period of 18-24 months. One patient lost only 49.5 kg. in a period of four and one-half years. Seven patients required cholecystectomy since surgery for by-pass.

TABLE I

UNTOWARD RESULTS ALL IN FIRST GROUP

	Patients	Per cent
Diarrhea	20	67
Abdominal distention	7	23
Excesseive loss of weight	2	9
Wound dehiscence	1	3
Failure to lose weight	1	3

Electrolyte imbalance was not a problem in this group of patients, with the exception of two who had severe hypokalemia, due to abuse of diuretics. In 12 patients serum proteins (Table II) dropped to

TABLE II

Serum Protein and Enzyme Alterations
First Group (30 Patients)

	Range	Number of patients
Serum protein	6-6.2 gm.%	12
Serum albumin	3-4 gm.%	12
Beta globulin	0.60-1.16 g/dl	12
Gamma globulin	1-2.2 g/dl	30
SGOT	58-40 gm.%	15
LDH	200-275 gm.%	15
Alkaline phosphatase	102-150 gm.%	15

Second Group (90 Patients)

	Range	Number of patients
Serum protein	6-6.5 gm.%	6
Serum albumin	3.2-3.5 gm.%	6
Beta globulin	0.40-1.0 g/dl	6
Gamma globulin	0.82-1.90 g/dl	80
SGOT	35-40 gm.%	6
LDH	125-150 gm.%	6
Alkaline phosphatase	70-80 gm.%	6

levels between 6.0 and 6.2 gm.% with marked reduction of albumin which persisted for three weeks to ten months postoperatively. After one year they all had returned to normal and the gamma globulin rose above normal levels in almost all of the patients. From three weeks to ten months after surgery, increase in SGOT, LDH and alkaline phosphatase was noted in 15 patients.

In the second group of 90 patients in which a modified technic was used, diarrhea was minimal and most had only one bowel movement per day. Weight loss was not as rapid as in the first group but they reached the same average level. There were no problems with electrolyte imbalance. In six patients, serum proteins fell below normal levels four to six months after surgery without clinical manifestation and returned to near normal levels within the next 12 months. While a decrease in serum albumin and beta globulin has been noticed, no change in gamma globulin was demonstrated. Serum cholesterol and lipids decreased almost immediately after surgery. Blood sugar levels in the "diabetic" patients returned to normal levels after surgery and insulin therapy was discontinued (Table II).

Comment

Since 1970, we have felt that the surgical approach to this problem is encouraging and the results are physiologically acceptable, especially in the second group of patients in which we used 35 cm. proximal limb and 20 cm. distal limb with drainage of the by-passed intestine into the cecum. With this method, maintainance of weight reduction by creating an assimilation deficit was accomplished while allowing relaxation of dietary restrictions.

It has been gratifying that drainage of the by-passed segment into the cecum has enhanced reabsorption of fluid and electrolytes and that the length of bowel employed has prevented liver damage while resulting in satisfactory weight loss.

Conclusions

Intestinal by-pass may be performed as a last resort in the treatment of morbid obesity in highly selected patients and after careful clinical, radiological and psychiatric evaluation.

Intestinal by-pass, accomplished by anastomosing the proximal 35 cm. to the distal 20 cm. of small bowel with drainage of the by-passed segment into the cecum can be performed with the same mortality and morbidity of any major abdominal procedure and with minimal undesirable side-effects and few long-term complications.

Liver and nutritional deficiencies are still incompletely explained requiring further study but they decrease during the first year following surgery.

The reduction of serum cholesterol, lipids and blood sugar are immediate.

The results of surgical treatment of morbid obesity are still variable and not altogether predictable. The modality deserves further study.

ACKNOWLEDGMENT

The authors are of the opinion that the remarkable absence of mortality in this series is largely due to the excellent care given these patients by the resident staff at St. Joseph's Infirmary.

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Clinical and Pathological Spectrum of Antibiotic-associated Colitis

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Antibiotic-induced colitis is a well recognized entity. It has been associated with the use of ampicillin, tetracycline, chloramphenicol, lincomycin, and most recently clindamycin.[1-16] The spectrum of symptomatology varies widely from mild diarrhea to fulminating diarrhea with electrolyte imbalance, dehydration, and death. Endoscopic findings range from simple edema and easy friability to ulceration, submucosal nodules and pseudomembrane formation. Clindamycin has been the most recent offending antibiotic receiving attention but other antibiotics are still frequently involved. In the past 15 months we have seen 11 cases of pseudomembranous colitis related to the use of various broad spectrum antibiotics used singly or in combination. We have included our two patients previously reported[1] who died and nine new cases to emphasize the wide clinical and pathological spectrum of this disorder and to stress that early recognition with prompt discontinuance of the offending antibiotic is imperative.

CASE REPORTS

Case 1:—A 19-year old woman underwent a total left hip replacement for severe juvenile rheumatoid arthritis which she had had since age 5. She had been treated previously with steroids and gold. One day postoperatively she developed a fever of 39° C and was placed on clindamycin 600 mg. intravenously every 12 hours and cephalothin 2 gm. intravenously every six hours for six days. Diarrhea began 72 hours after initiation of the antibiotic treatment. Gram stain of the stool showed mixed flora and a few white blood cells but no staphylococci. Her WBC was 19,600 with 69% polymorphonuclear leucocytes and 20% band forms. Colonoscopy was performed six days after stopping antibiotics and showed granular mucosa from the rectum to the splenic flexure with superficial ulcerations and patchy inflammation. Biopsy showed an acute inflammatory reaction and mild edema of the colonic mucosa. She gradually improved and was discharged on the 18th postoperative day without diarrhea.

Case 2:—An 82-year old man had chronic lymphocytic leukemia and recurrent staphylococcal skin infections. He had been receiving prednisone 30 mg. every other day and clindamycin 150 mg. orally

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twice a day for four months. Two days prior to admission he experienced diarrhea and weakness. His WBC was 4,500. Barium enema showed diffuse, small nodular mucosal lesions throughout the colon. Sigmoidoscopy to 15 cm. showed edema. Colonoscopy showed multiple submucosal nodules in the descending, transverse and ascending colon with surrounding erythematous areas. Biopsy showed mucosal edema with small nondiagnostic lymphoid nodules in the mucosa and submucosa. Stool cultures were negative. Clindamycin was discontinued and prednisone was increased to 20 mg. daily. The diarrhea subsided promptly and the patient was discharged on the ninth hospital day.

Case 3:—A 69-year old man was treated with clindamycin for three days for cough and sore throat. Diarrhea of five to six watery bowel movements, suprapubic cramping, and fever of 39° C developed shortly thereafter. Cultures were negative for ova, parasites, and staphylococci. A WBC was not performed. Barium enema was normal. Colonoscopy was performed six weeks after the onset of diarrhea. The rectosigmoid colon to the transverse colon showed patchy areas of slightly raised nodules with small central ulcerations. The distal sigmoid colon showed areas of patchy membrane formation with superficial ulcerations. Seven weeks after the onset of symptoms bowel movements were normal.

Case 4:—A 34-year old man was treated with chlortetracylcine 250 mg. four times a day for five days for a sore throat. Acute onset of diarrhea with bloody mucoid stools and lower abdominal cramps began four days after the initiation of antibiotic treatment. He was afebrile and his WBC was 11,000. Stool cultures for staphylococci, ova and parasites were negative. Barium enema showed prominent edematous haustra throughout with slight mucosal irregularity in the sigmoid colon suggestive of ulceration. Colonoscopy was performed to the hepatic flexure and showed patchy, inflammatory reaction at the rectosigmoid junction with marked edema and moderate friability to the transverse colon. There were a few small ulcerations scattered throughout the bowel. Biopsy showed subacute inflammation. His symptoms subsided two weeks after the onset.

Case 5:—A 70-year old man was taking ampicillin 500 mg. orally four times a day for six days and then 250 mg. four times a day for prostatitis and a urinary tract infection. One week prior to admission he began having diarrhea with 12-20 bowel movements per day with cramping but no bleeding. His abdomen was nontender; bowel sounds were hyperactive. His WBC was 13,000. Ampicillin was stopped and gentamycin was begun. Sigmoidoscopy to 16 cm. showed edema and erythema. Colonoscopy to the splenic flexure, performed five days after stopping ampicillin, showed edema and patchy areas of small ulcerations. Barium enema revealed submucosal infiltration throughout the entire colon. Colonic biopsy showed mild chronic inflammation with congestion and edema of the mucosa. Stool cultures were negative. Diarrhea subsided one week after cessation of ampicillin.

Case 6:—A 17-year old man was treated with ampicillin 250 mg. four times a day for five days for an upper respiratory infection one week prior to admission. Three days after starting ampicillin he experienced lower abdominal pain and five watery bowel movements per day, containing mucopus and streaks of blood. He was afebrile and his WBC was 8,900 with 60% polymorphonuclear cells. Stool cultures were negative. Barium enema demonstrated large haustra in the descending colon and nodular mucosa in the sigmoid and descending colon. Colonscopy was performed to the splenic flexure four days after the onset of symptoms. There was a patchy inflammatory process involving approximately 40% of the mucosal surface in the distal sigmoid colon. There was edema with easy friability, superficial ulcerations and early pseudomembrane formation. The process extended to a lesser degree to the splenic flexure. He was treated with Azulfidine®* 4 gm./day and prednisone 20 mg./day and a low residue diet. Ampicillin was discontinued and within two weeks he was asymptomatic.

Case 7:—A 69-year old man underwent an elective total left hip replacement for degenerative joint disease and septic hip. He received clindamycin 600 mg. and cephalothin 2 gm. every six hours prior to surgery. He developed diarrhea and abdominal distention with dysuria and fever of 40° C on the fifth postoperative day. He subsequently developed hematest positive stools and a WBC of 80,000 with 80% polymorphonuclear cells and a sodium of 119 mEq./l. and a potassium of 5.0 mEq./l. He was treated with steroids without response. Clindamycin was discontinued on the seventh postoperative day but cephalothin was continued. Blood, urine and stool cultures were negative. Sigmoidoscopy was not performed. The patient suffered a cardiac arrest and expired on the tenth postoperative day. Necropsy showed a grey-green pseudomembrane with small ulcerations and inflammatory infiltrate and dilatation of the entire colon.

Case 8:—A 73-year old man sustained an injury to his left knee. He was admitted to the hospital with a temperature of 39° C and a pulse of 110/min. Ampicillin 1 gm. every four hours was begun intravenously for suspected urinary tract infection. Penicillin was substituted for the ampicillin when a streptococcal infection was suspected. This was then changed to vancomycin 1 gm. every 12 hours because of a urinary enterococcal infection. The patient developed a rash and cultures confirmed a nonenterococcal alpha-streptococcus and therefore cephalothin 2 gm. every four hours was substituted for the vancomycin. His fever, however, persisted and clindamycin 400 mg. every six hours was begun intravenously and cephalothin was discontinued because of a possible drug fever. The dose was decreased to 300 mg. every eight hours intravenously and then switched to the oral route. Diarrhea began on the 34th hospital day, six days after the initiation of clindamycin. The patient expired quietly on the 48th hospital day Necropsy showed a dilated colon with pseudomembrane formation and small ulcerations and inflammatory reaction throughout the colon.

Case 9:—A 49-year old woman who was diabetic with atherosclerotic heart disease was admitted for cataract extraction. She had been on erythromycin 250 mg. three times a day for a long period for a chronic foot ulcer. She underwent a right cataract extraction and two days postoperatively she developed a fever of 40° C with a white blood cell count of 18,000. She had bibasilar rales on the third postoperative day and was started on clindamycin 300 mg. intravenously every four hours. She had a persistent tachycardia of 100/min. A left pleural effusion developed and a sterile transudate was aspirated. On the 28th postoperative day her abdomen was nontender but distended and tympanitic. She expired on the 35th hospital day of a cardiac arrest. Necropsy showed a membranous colitis throughout the colon but more marked in the ascending colon and terminal ileum.

Case 10:—A 46-year old woman underwent a total right hip replacement of a possible septic joint. Postoperatively cephalothin 2 gm. and clindamycin 600 mg.

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* Pharmacia Laboratories, Piscataway, NJ.

TABLE I

Spectrum of Antibiotic-induced Colitis

Case age, sex	Antibiotic	Indication	Other medical problems	WBC	Colonoscopy	Barium enema
1. 19 F	clindamycin cephalothin	hip replacement	rheumatoid arthritis	19,600	granularity, ulcerations, patchy inflammation	not done
2. 82 M	clindamycin	recurrent staphylococcal infections	chronic lymphocytic leukemia	4,500	submucosal nodules	small nodular mucosal lesions
3. 69 M	clindamycin	upper respiratory infection	none	not done	nodules, ulcerations, membrane	unremarkable
4. 34 M	acromycin	upper respiratory infection	none	11,000	patchy inflammation, edema, ulcerations, friability	edematous haustra, mucosal irregularity
5. 70 M	ampicillin	prostatitis, urinary tract infection	none	13,000	edema, ulceration	submucosal infiltration
6. 17 M	ampicillin	upper respiratory infection	none	8,900	edema, ulcerations, friability, mucosal inflammation	edematous haustra, mucosal nodules

TABLE I

SPECTRUM OF ANTIBIOTIC-INDUCED COLITIS *(continued)*

Case age, sex	Antibiotic	Indication	Other medical problems	WBC	Colonoscopy	Barium enema
7. 69 M	clindamycin cephalothin	total hip replacement	degenerative joint disease	80,000	not done	not done
8. 73 M	ampicillin penicillin vancomycin cephalothin clindamycin	urinary tract infecton iliopsoas abscess	ASHD hypertension diabetes mellitus alcoholism glaucoma	9,700	not done	unremarkable
9. 49 F	erythromycin clindamycin	chronic foot ulcer, possible pneumonia	cataracts diabetes mellitus congestive heart failure	18,000	not done	not done
10. 46 F	clindamycin cephalothin	septic joint	none	19,300	thick mucous membrane, granularity, friability	not done
11. 71 M	lincomycin	hip replacement	none	24,000	edema, granularity, inflammation, membrane	not done

every 6 hours were begun intravenously. On the ninth post operative day she developed a temperature of 39° C, nausea, vomiting, abdominal cramps and bloody diarrhea. Flat film of the abdomen was unremarkable. Stool cultures were negative for organisms but showed many white blood cells. Peripheral WBC was 19,300 with 83% polymorphonuclear leucocytes. Colonoscopy was performed to the descending colon and showed thick confluent pseudomembrane in the rectosigmoid colon. There was mild granularity and friability with bleeding at the sites where the membrane was removed. She received prednisone orally 40 mg./day with decreasing dosage over a week's period. The diarrhea subsided 18 days after discontinuing antibiotics.

Case 11:—A 71-year old man received six doses of lincomycin 600 mg. intravenously after hip surgery. On the fifth postoperative day he developed a fever to 38.3° C and a WBC of 24,000. On the eighth postoperative day he developed watery diarrhea with three to four bowel movements per day which lasted for seven days. On the ninth postoperative day his temperature returned to normal. Stool cultures for ova, parasites and bacteria were negative. Barium enema was not performed. Colonoscopy to the mid ascending colon showed edema, granularity and inflammation with a pseudomembrane in the sigmoid, descending and transverse colon which were less pronounced in the proximal colon.

COMMENT

Antibiotic-associated colitis received early attention in the 1950's after the introduction of broad-spectrum antibiotics,[11, 12] and has again achieved considerable clinical importance with the introduction of lincomycin and most recently its analogue clindamycin.[1-10, 13-15] Both of these antibiotics have now been clearly implicated as agents capable of producing colitis. In a prospective study, diarrhea was found to occur in 21% of patients receiving clindamycin and pseudomembranous changes occurred in 10%.[2] Clindamycin was used as the sole antibiotic in only two of our cases while six received clindamycin in association with a variety of other antibiotics, either sequentially or in combination, prior to the onset of symptoms (Table I). Despite the frequent occurrence of clindamycin-associated colitis, the physician prescribing antibiotics should not forget the occurrence of colitis with other broad-spectrum antibiotics.[4-6, 9-12]

As in other reports the method of administration was of no importance,[2] since the colitis developed in patients receiving antibiotics orally and parenterally. It is noteworthy that in several instances antibiotics were used for simple upper respiratory infections and frequently the offending organism was not isolated.

The clinical spectrum ranges from one of mild diarrhea to fulminant diarrhea with fever, dehydration and death. A fatal course occurred in three of our patients. The absence of deaths in the patients with pseudomembranous colitis reported by Tedesco, et al[2] is probably related to early recognition and prompt treatment. The diarrhea in antibiotic induced colitis usually has no specific features and is only occasionally accompanied by hematochezia. Abdominal pain and fever are commonly encountered in the more seriously ill patient. In some patients there is marked abdominal distention due to a dilated colon and a picture similar to a toxic megacolon has been reported.[17] Two of our three patients who died demonstrated marked colonic distention at autopsy. Twenty to thirty per cent may have this colonic dilatation without diarrhea.[2] Laboratory studies may show leucocytosis and electrolyte abnormalities. Examination of the stool shows large numbers

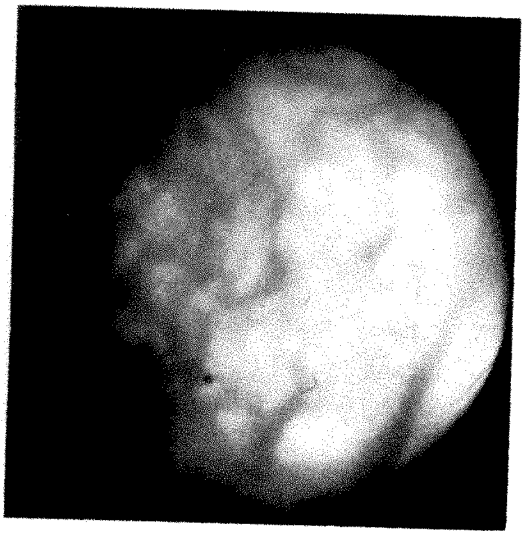

Fig. 1—Midsigmoid colon. There is total loss of the normal sigmoid valve pattern. The mucosal surface is covered by a dense patchy grey-white membrane. The cobblestoned appearance is due to mucosal edema.

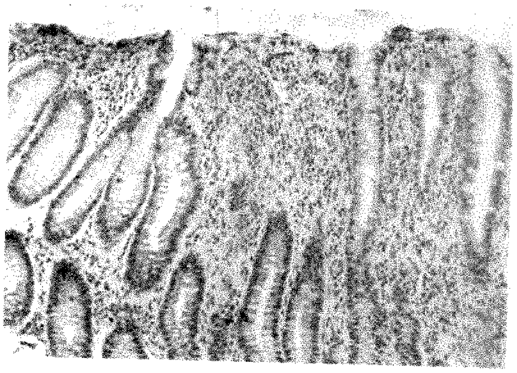

Fig. 2—Colon biopsy shows the very early changes in pseudomembranous colitis with minimal necrosis of the columnar cells and infiltration of lymphocytes in the interstitium (original magnification x125).

of leucocytes and cultures reveal normal colonic flora without staphylococci. Symptoms usually begin two to 14 days after instituting antibiotics. In most instances diarrhea lasts two to six weeks after the antibiotics have been discontinued. In a small percentage of patients with milder, more limited disease the symptoms may subside within a few days.

Sigmoidoscopy was performed in only two of our patients and showed marked edema and erythema of the rectum and rectosigmoid colon without membrane formation or ulceration. In both cases the disease process extended beyond the reach of the sigmoidoscope. Colonoscopy was performed at least to the splenic flexure in seven cases and showed involvement of the colon to this level or beyond in all seven. Abnormalities ranging from mucosal edema with marked friability and ulceration to diffuse pseudomembrane or patchy membrane formation with or without nodularity and ulceration were encountered. In all cases the severity of the disease decreased in the more proximal portions of the colon. The extent of the abnormalities usually correlated with the severity of the patient's illness. Figure 1 shows an endoscopic view of the mid sigmoid colon. There is total loss of the normal sigmoid valve pattern and the mucosal surface is covered by a dense patchy grey-white membrane.

Seven patients had barium enemas. In the remaining four, recent orthopedic procedures made it impossible. Where done, the barium enema demonstrated mucosal edema, ulcerations and nodularity in varying combinations in five cases while the barium enema was normal in two cases These abnormalities are similar to those reported by others.[8, 13-15] A picture similar to toxic megacolon was reported by Tully and Feinberg[17] following barium enema. A markedly dilated colon was found at autopsy with pseudomembranous changes in two of our patients. Lesions resembling plaques have been described in some cases[13] and were felt to be a specific radiographic abnormality. Such plaques were not encountered in our patients. Generally the abnormalities have been those seen in inflammatory bowel disease. The normal barium enema encountered in our patients

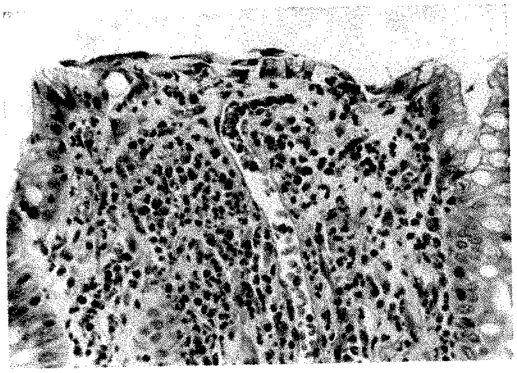

Fig. 3—Higher power view of Figure 2 shows more clearly the early necrosis and lymphocytic infiltration (original magnification x300).

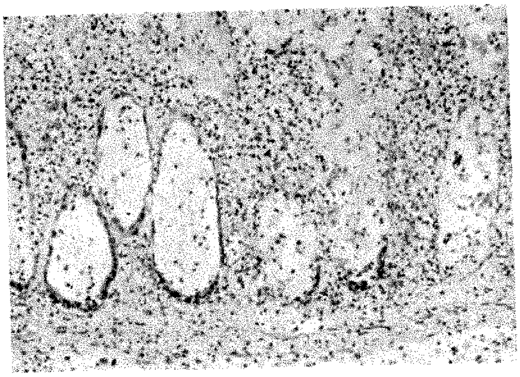

Fig. 4—Colon biopsy shows late changes of diffuse necrosis and deposition of necrotic tissue in the interstitium with loss of cryptic structure with minimal preservation of the cells along the base of the crypts (original magnification x125).

has also been noted by others.[6] When abnormalities are present, they may involve only the rectosigmoid colon or the entire colon. In our experience colonoscopy better delineates the extent and severity of the disease than barium enema.

Histologically the affected areas demonstrate acute and chronic inflammation with or without ulceration and may also present an appearance similar to inflammatory bowel disease. The development of a membrane which is tightly adherent over ulcerated mucosa distinguishes it from other types of inflammatory bowel disorders (Figs. 2, 3 and 4).

Therapy of antibiotic-induced colitis depends principally on the initial recognition of the disorder and prompt discontinuance of the offending antibiotic. Proper maintenance of electrolyte and fluid balance is imperative since the deaths that occur are invariably due to electrolyte imbalance and shock resulting from dehydration. Oral steroid therapy was used in three of our patients with no apparent benefit. Since the inflammatory process usually extends above the rectosigmoid colon, administration of steroids by enema should also be without significant effect. Recently cholestyramine has been used in two patients with very rapid clinical improvement.[18]

CONCLUSION

The spectrum of antibiotic-induced colitis is varied both clinically and pathologically and may be seen with a variety of antibiotics. Our study and others indicate the need for a more careful approach to the administration of antibiotics and knowledge of their effects on the gastrointestinal tract. Their use in patients with probably viral infections should be avoided as should the use of antibiotics with a high incidence of serious toxic effects on the colon except in those patients in whom appropriate bacterial studies or clinical situations indicate the necessity of their administration. If diarrhea develops in any patient receiving antibiotics, they should be stopped immediately. Diagnostic procedures should include barium enema, sigmoidoscopy and/or colonoscopy. Supportive therapy with fluids and electrolytes should be instituted.

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Clinical Vignette

Granuloma (Sarcoid?) of the Pancreas

A CASE REPORT

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Clinically apparent pancreatic disease due to sarcoidosis has not been described in typical sarcoid patients. A few cases have been described at exploratory laparotomy and pancreatic involvement in autopsied cases is more common than generally appreciated. We report a patient not previously known to have sarcoidosis whose presentation with pruritus, eosinophilia and cholestatic serum chemistry suggested a reaction to phenothiazines. The correct diagnosis was made during surgery for an asymptomatic gallstone. No other evidence of pancreatic disease has become apparent during follow-ups of two years.

Pancreatic sarcoidosis is rarely detected in life and the nonoperative diagnosis has not been reported. While reported cases have been manifest by pancreatic insufficiency, diabetes or obstructive jaundice, we have seen a patient whose initial presentation suggested a cholestatic drug reaction.

CASE REPORT

A 37-year old black male was referred because of pruritus of one year's duration, unresponsive to topical treatment. He was found to have an elevated alkaline phosphatase and was admitted for further study in October, 1973. He denied abdominal pain, weight loss, jaundice and other digestive symptoms. Sickle cell trait had been detected several years previously. There was no history of alcoholism or hepatotoxin exposure. After admission he admitted using Temaril (trimeprazine) for about four months without relief of pruritus. Physical examination was negative except for a nondescript faint papular eruption. No lymph node or organ enlargement was found.

Laboratory study disclosed 10% elevation of the eosinophil count; alkaline phosphatase of 13 (normal 1.2-4.2); SGOT, 67 (0-40) and amylase, 126 (20-100). Icterus index was 3 and the 45-minute retention of BSP was 25%. Chest x-ray showed no abnormalities and abdominal echogram, liver-spleen scan and gastrointestinal x-rays were negative except for a solitary gallstone. Percutaneous liver biopsy showed only periportal eosinophilic infiltration. A diagnosis of cholestasis due to phenothiazine was made and he was discharged without therapy to return in several weeks for consideration of elective cholecystectomy.

He returned with continued pruritus in February, 1974, four months after phenothiazine withdrawal; cholestasis and eosinophilia persisted. Repeat x-rays, echogram and scans were unchanged. Bone marrow examination and oral glucose tolerance test

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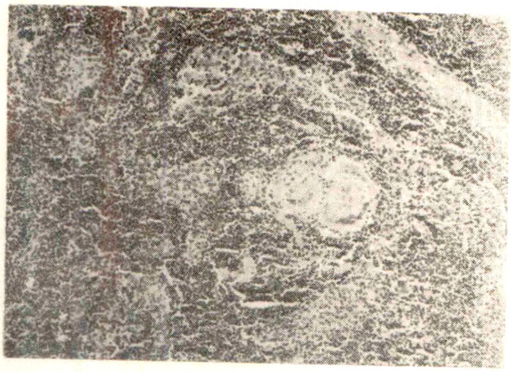

Fig. 1—Section of peripancreatic lymph node showing noncaseating granuloma and giant cells (Hematoxylin and eosin, original magnification x100).

were normal. Cholecystectomy and exploration of the common duct were advised. At surgery, a single stone was found in the gallbladder, which was removed and the common duct appeared normal. The pancreas was firm and slightly enlarged and large peripancreatic nodes were found around the head of the pancreas and the common duct. Biopsies of the liver and nodes were taken. The liver was normal, but the nodes showed numerous noncaseating granulomas and no other abnormalities (Fig. 1). Postoperatively the patient had fever, pleural effusion and hyperamylasuria for several days. When this resolved, he was discharged on cholestyramine and arrangements made for further study after he had completed convalescence.

In June, 1974, he returned and reported improvement in pruritus. Alkaline phosphatase was elevated only slightly. Intradermal tests showed no reaction to intermediate PPD and 20 mm. induration at the site of histoplasmin injection. A Kveim test was performed and later biopsy showed no granulomata. Pulmonary function tests, quantitative fecal fats, secretin test and multiple skin biopsies were all normal. He has continued to have only mild pruritus relieved by cholestyramine and no new digestive symptoms have appeared during two year follow-up.

Comment

Five instances of pancreatic involvement were found in the 92 autopsied cases of sarcoidosis reviewed by Longcope and Freiman.[1] None of these had clinical evidence of pancreatic disease. Three additional reported cases found at exploratory laparotomy had symptoms of abdominal pain and weight loss. One had only steatorrhea,[2] one had diabetes, jaundice and a palpable gallbladder[3] and the third showed BSP retention, elevated SGOT and alkaline phosphatase and developed hyperglycemia postoperatively.[4] None was known to have sarcoidosis prior to surgery and only one had radiographic evidence of hilar adenopathy. The Kveim test was positive in a single patient in whom it was done, whose chest x-ray was normal.

Elevation of the alkaline phosphatase and BSP retention in a patient known to have sarcoidosis would ordinarily be attributed to hepatic involvement. Although hepatomegaly and liver granulomas are frequent findings in sarcoidosis, clinically important liver disease is uncommon.[5] Our patient, whose liver function tests showed cholestasis, had no liver granulomas on two biopsies and adequate explanation for these abnormalities was found in the pancreatic disease discovered at surgery. The atypical clinical and radiographic features, the absence of hilar adenopathy and the lack of evidence for involvement of other organs raise some doubts regarding the accuracy of the diagnosis of sarcoidosis in the surgical patients. On the other hand, early autopsy studies described pancreatic involvement in about 6% of otherwise typical cases. Perhaps pancreatic granulomas should be considered as an alternative or additional cause of abnormal tests of liver function in patients with typical sarcoidosis.

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Clinical Vignette

Congenital Duodenal Stenosis

THE DUODENAL CERVIX SIGN

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A case of congenital duodenal stenosis is reported complicated by recurrent pancreatitis. The diagnosis was not initially entertained because of the pancreatitis. The radiographic appearance on gastrointestinal series was unusual for pancreatitis. The finding of an anomalous celiac axis on arteriography suggested the possibility of other congenital anomalies. The diagnosis of congenital duodenal stenosis was confirmed at laparotomy. The obstruction was relieved with a duodenojejunostomy. Two year follow-up reveals the patient to be asymptomatic without recurrence of pancreatitis. This is the first endoscopic report of this lesion and the presence of the duodenal cervix sign should suggest the diagnosis of congenital duodenal stenosis.

Symptomatic congenital malformations of the upper gastrointestinal tract are more commonly seen in infancy. Clinically, however, silent congenital malformations of the upper gastrointestinal tract may become symptomatic in adult life and may create a diagnostic problem. Congenital lesions of the gastroduodenal region are classified as: congenital bands,[1] annular pancreas,[2] duodenal diaphragm,[3] Wilkie's syndrome[4] and congenital duodenal stenosis.[5-7]

This case report of congenital duodenal stenosis demonstrates an unusual endoscopic appearance and an associated anomaly of the hepatic artery.

CASE REPORT

A 37-year old, black male was admitted in May, 1974 for intermittent epigastric pain, postprandial fullness and vomiting of nine months' duration. Two consecutive hospital admissions nine months previously were for pancreatitis and alcoholic hepatitis. A gastrointestinal series showed megaduodenal bulb and narrowing of the apex of the duodenal bulb. Upon hospital discharge he continued to have the above symptoms which failed to respond to antacids and anticholinergics. A 16.65 kg. weight loss ensued over the past year. There was no hematemesis or melena.

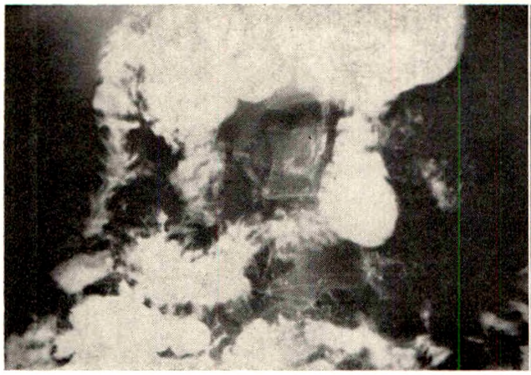

Fig. 1a

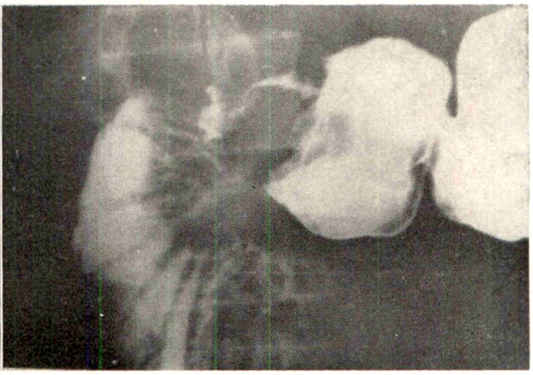

Fig. 1b

Figs. 1a and 1b—Megaduodenal bulb, deformity and irregular narrowing of the apex of the bulb causing delay of barium passage into the duodenal sweep.

Follow-up upper gastrointestinal series six months prior to the present admission was basically unchanged.

His physical examination was generally negative except for epigastric tenderness on palpation. The initial laboratory values were essentially within normal limits except for the serum amylase which was in the range of 250-200 units and serum lipase which was 2.5-2. His liver profile, total protein, albumin, prothrombin time and CBC were within normal limits.

The patient was treated conservatively for acute pancreatitis. The serum amylase and lipase values returned to normal during a two-week period. He continued to have intermittent epigastric pain and vomiting.

An upper gastrointestinal series showed (Figs. 1a and 1b) megaduodenal bulb, deformity and irregular narrowing of the apex of the bulb causing delay of barium passage into the duodenal sweep. The x-ray findings were similar to those seen one year ago. Oral and I.V. cholangiogram were normal.

Endoscopic examination revealed (Fig. 2) a narrowed, nipple-shaped lumen (5 mm. diameter) at the apex of the duodenal bulb with circumferential cuffing of the duodenal mucosa giving the appearance of a cervix. There were no erosions or friability in the narrowed lumen. Repeated examinations revealed no variation in this appearance after intravenous glucagon. Celiac angiography showed trifurcation of the celiac axis into a splenic artery, dorsal pancreatic artery and a gastroduodenal artery. The hepatic artery had its origin from the gastroduodenal artery and was moderately narrowed. The blood supply to the liver was scant. No other arteries perfusing the liver could be identified on the superior mesenteric angiogram.

On the 22nd day of hospitalization an exploratory laparotomy was performed. It was noted that the first part of the duodenum was distended and just distal to it and above the papilla of Vater, there was a circumferential noninflammatory submucosal constriction measuring 3 mm. in width (Fig. 3). There was no pancreatic tissue around this constriction. Pancreas was normal on palpation. Duodenojejunostomy was performed to by-pass the stenotic lesion. Review of the literature by Raquel[5] indicates this was the operation most frequently performed. The post-operative course was uneventful. The patient remained asymptomatic after a two-year follow-up.

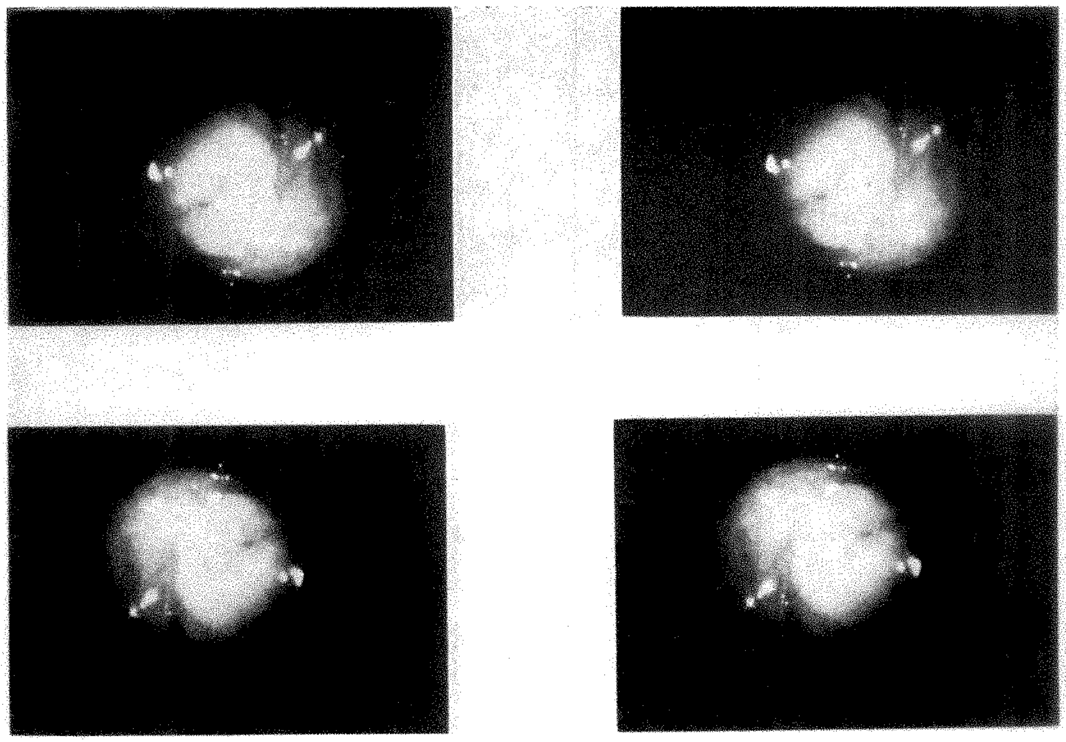

Fig. 2—Endoscopic examination of a narrowed nipple-shaped lumen at the apex of the duodenal bulb with circumferential cuffing of the duodenal mucosa giving the appearance of a cervix.

TABLE I

Extrinsic causes	Intrinsic causes
(A) Not associated with faulty mid gut rotation:	Duodenal stenosis
Annular pancreas	Duodenal diaphragm
Peritoneal folds	
Occluding veins	Enterogenous cyst
Duodenum diverticulum	*Megaduodenum congenitum*
(B) Associated with faulty mid gut rotation:	
Paraduodenal hernia	
Volvulus	
Wilkie's syndrome	
Abnormally positioned proximal colon	

COMMENT

Congenital obstructive lesions of the duodenum are classified as shown in Table I.

The most common site of intrinsic malformation in the gastrointestinal tract is the duodenum. Involvement of the proximal duodenum by intrinsic malformation is rare compared to the distal duodenum. This case is unusual in that stenosis was proximal in location and the clinical symptoms presented at the age of 36. The associated ethanolism and pancreatitis initially complicated the clinical course and indeed delayed the diagnosis of the congenital duodenal stenosis. The continuation of abdominal symptoms after two weeks, with the return to normal of the amylase and lipase values and the demonstration of the proximal duodenal stenosis on x-ray, led to the suspicion of a pancreatic inflammatory stricture. Acute pancreatitis may cause intestinal obstruction and may involve the duodenum or jejunum.[8, 9] The cause of obstruction may be due to an edematous pancreatic mass, peripancreatic inflammation or encroachment by a pseudocyst. Duodenal obstruction secondary to pancreatitis is rare and usually involves the second portion of the duodenum.[10] The finding of a 3 mm. submucosal band without inflammation makes it unlikely that this was due to pancreatitis.

The literature indicates that some patients with CDS may have associated pancreatitis as with annular pancreas. It is possible in this case that the CDS was contributory to the pancreatitis. Further follow-up will help clarify the etiological role of CDS in this patient's pancreatitis.

Congenital duodenal stenosis has its origin in embryonal development. Raquel[5] has reviewed the literature of the embryonal origin of the lesion of congenital duodenal stenosis, atresia or diaphragm which may be from developmental arrest of the duodenum during the second and third months of fetal life. The incidence of other congenital lesions associated with congenital duodenal stenosis is not known. Thirty per cent of the children with intrinsic duodenal obstruction have Down's syndrome in Sachs and Feldman's report.[11] Longo and Lynn[6] reported 12 cases of congenital duodenal stenosis of which five were adults, three of whom had other associated abnormalities which include either coarctation of aorta, incomplete rotation of the gut, congenital heart disease or microcephaly.

A congenital anomaly of the celiac axis was demonstrated in our case. The arterial blood supply to the liver was diminished and a right hepatic artery was not demonstrated on celiac and superior mesenteric arteriography. This vascular anomaly has been described by Ruzicka and Rossi,[12] Suzucki, Nakayasu, Kawabe, et al[13] and French.[14]

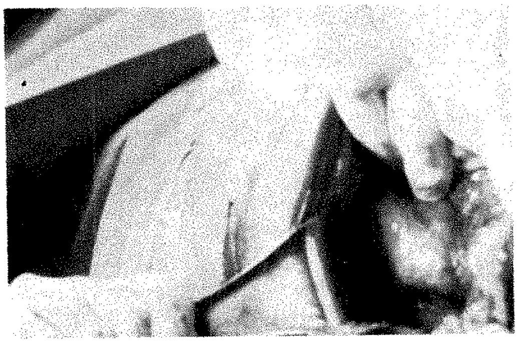

Fig. 3—A circumferential noninflammatory stenosing lesion of 3 mm. width between the first and second portions of the duodenum seen on an exploratory laparotomy.

The endoscopic appearance was unusual in that the duodenal bulb was dilated and the area of stenosis simulated a human cervix. The fixed stenotic nature was confirmed by failure to relax with intravenous glucagon. This endoscopic appearance in congenital duodenal stenosis, the duodenal cervix sign, in our search of the literature has not been previously reported and may be diagnostic of this lesion. A similar sign has been described in congenital pyloric stenosis termed the pyloric cervix sign by Schuster and Smith.[15].

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Clinical Vignette

Granulomatous Ileocolitis Preceded by Three Years of Pauciarticular Arthritis

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The case of a 12-year old male is presented in whom pauciarticular arthritis preceded the clinical onset of granulomatous ileocolitis by three years. Before the onset of gastrointestinal symptoms, the patient's clinical diagnosis was juvenile rheumatoid arthritis. This case stresses the importance of including inflammatory bowel disease in the differential diagnosis of pauciarticular arthritis in children.

The association of inflammatory bowel disease and arthritis is well known. More recent retrospective series have shown the incidence of arthritis in inflammatory bowel disease to be about 20%.[1, 2] The incidence is higher if one looks only at inflammatory disease of the colon.[3] A recent review of children with inflammatory bowel disease has shown a 17% association.[4]

Although uncommon, inflammatory bowel disease initially may present solely with articular symptoms. The following report describes a 12-year old male presenting pauciarticular arthritis three years before the clinical onset of granulomatous ileocolitis. The prolonged arthritic prodome, clinically indistinguishable from juvenile rheumatoid arthritis, before the onset of gastrointestinal symptoms prompted this case report.

CASE REPORT

A previously healthy 12-year old white male sought medical attention for a swollen, painful right ankle. Clinical and laboratory investigations at this time were unremarkable except for an erythrocyte sedimentation rate of 47mm./hr. and a tender right ankle joint containing some fluid and a thickened synovium. The latex fixation rheumatoid factor was negative. A presumptive diagnosis of juvenile rheumatoid arthritis was made. Casting of the afflicted joint and anti-inflammatory doses of aspirin failed to completely relieve the ankle swelling or the patient's discomfort. Synovial biopsy of the right ankle showed evidence of chronic synovitis. Transient mild pain and stiffness of both hips and the left elbow occurred.

Over the next two years the patient exhibited normal growth and had no complaints other than minimal ankle stiffness. He then became completely asymptomatic and salicylates were discontinued. Six months later the right ankle again became swollen, warm and tender. Aspirin was re-

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started after another physical and laboratory examination again revealed only an elevated sedimentation rate and similar ankle findings. On aspirin he became asymptomatic and remained so for the next six months.

He was seen again three years after the initial evaluation with a six-week history of a 4.5 kg. weight loss, malaise, anorexia, episodic right lower quadrant discomfort and watery stools. A right lower quadrant mass, 4 cm. in diameter, was palpated. Radiographs of the large and small intestines showed marked narrowing, submucosal thickening and rigidity of the terminal ileum, cecum and ascending colon with a fistula connecting the distorted cecum and the narrowed terminal ileal segment. These findings were felt to be consistent with granulomatous ileocolitis. Sigmoidoscopy and rectal biopsy were normal.

A short course of prednisone plus continued salicylazosulfapyridine therapy produced a good clinical response. The patient's weight increased, the right lower quadrant mass decreased in size and tenderness and the diarrhea ceased. The patient's right ankle remained unchanged with minimal swelling, warmth, and tenderness. He remains in remission from his bowel disease now one year after the onset of his bowel symptoms.

COMMENT

For three years this patient was presumed to have juvenile rheumatoid arthritis. Approximately one-third of juvenile rheumatoid arthritis patients present with mono- or pauciarticular disease of the large joints, most frequently the knees, ankles and elbows.[5] This type of juvenile rheumatoid arthritis frequently runs a protracted course, causes little disability or joint destruction, and is associated with few systemic symptoms.[5, 6] Since the rheumatoid factor frequently is not developed in children and there are no other definitive laboratory studies, the diagnosis remains founded on clinical grounds.

The diagnosis of colitic arthritis is also clinical and, in the absence of any bowel disease, is impossible. It is not readily distinguishable from arthritic joints of a variety of other diseases including rheumatoid arthritis.[4] Peripheral joint arthritis associated with inflammatory bowel disease most commonly begins abruptly in a large joint of the lower extremity but can at times involve the upper extremity or be in a migratory pattern.[2, 8] The episodes of arthritis are usually brief and self-limiting. They rarely lead to any destruction of the joint clinically or radiographically,[3, 8, 9] although Clark, et al,[10] found 28% of their patients had definite articular radiographic changes. Usually, the rheumatoid factor is negative.[11] Exacerbations of the arthritis tend to be associated with increased activity of the intestinal disease in adults[3, 8] but this has not been found in children[4] or in Crohn's disease.[11]

Clark, et al,[10] reported one patient who did present with severe Still's disease prior to developing ulcerative colitis. The length of time between these events was not specified. Arthritis can be the presenting symptom of inflammatory bowel disease but an arthritic course of three years prior to the gut symptoms is most unusual. Palumbo, et al,[3] retrospectively reported 121 cases of arthritis and inflammatory bowel disease. Of these only four cases had arthritic symptoms before the onset of the colitis. In these cases only several months transpired before the intestinal disease became evident. In two recent retrospective studies, six cases are mentioned where the initial presentation was arthritis. Two of these allegedly had arthritis symptoms six and eight years prior to the onset of intestinal symptoms, but detailed case histories are not given.[2, 4] A case report in 1968 of Crohn's disease presenting with acute polyarthritis has been discounted because the case probably was systemic *lupus erythematosus*.[2] One case from 1944 had rheumatic fever preceding the onset of Crohn's disease.[9]

This case again stresses the importance of including inflammatory bowel disease in the differential diagnosis of pauciarticular arthritis in children. One must include a careful clinical evaluation of the gastrointestinal tract when dealing with similar cases.

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The Radiology Corner*

MID ESOPHAGEAL STRICTURE

DAVID R. MUSHER, M.D., F.A.C.G.†
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A patient presented with a mid esophageal stricture. Clinical, radiological and histological studies led to a diagnosis of columnar-lined (Barrett) esophagus.

The squamous epithelium of the esophagus differs from that of the skin only by the absence of keratin and hair follicles. It responds to inflammation by scarring and is prone to the same disorders as skin, viz. *epidermolysis bullosa*, herpes simplex, pemphigoid and pemphigus. The squamous epithelium may be replaced partly or completely with columnar epithelium which may contain gastric glands, parietal cells, chief cells and clear mucus-secreting cells.[1]

The gastric-lined esophagus is either a congenital or an acquired abnormality. Imperfect embryogenesis which results in incomplete stratification of the esophagus and which leaves islands of squamous or columnar mucosa suggests the former. Emery and Haddadin[2] report an incidence of gastric epithelium lining the esophagus at the level of the mid trachea in 2.4% of routine autopsies performed in children and 34% of children with tracheoesophageal fistula and esophageal atresia. Their series included patients who had gastric epithelium within the atretic esophageal pouch. They concluded that gastric epithelium lining the esophagus is congenital and could not be acquired since one-half of their patients died within four days of birth.

On the other hand, the progressive development of columnar epithelium over a period of seven years in a patient with reflux esophagitis suggests an acquired condition.[3] Although the stratified squamous epithelium of the esophagus usually regenerates after injury, experiments in dogs revealed regeneration of columnar epithelium when denuded esophagus was perfused with acid.[4]

Barrett[5, 6] distinguished the rare gastric ulcer in the gastric-lined esophagus from the more common superficial peptic ulcerations associated with gastroesophageal reflux. The former, now termed a Barrett's ulcer or Barrett's syndrome, is a sharply demarcated, punched-out gastric-type ulcer located within the gastric mucosa in the esophagus. It may perforate, bleed, or form a stricture. The more common ulcerations occur at the gastroesophageal junction or within the squamous mucosa. They are usually superficial and rarely perforate.

Recent evidence associates the columnar lined esophagus with adenocarcinoma. Hawe, et al[7] reported five patients who presented with Barrett's esophagus and adenocarcinoma. An additional two out of 85 patients who presented with benign Barrett's esophagus subsequently developed adenocarcinoma and their review of the world literature suggests that Barrett's esophagus is a premalignant lesion. A re-

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* Edited by Richard H. Marshak, M.D., F.A.C.G. and Arthur E. Lindner, M.D., F.A.C.G.

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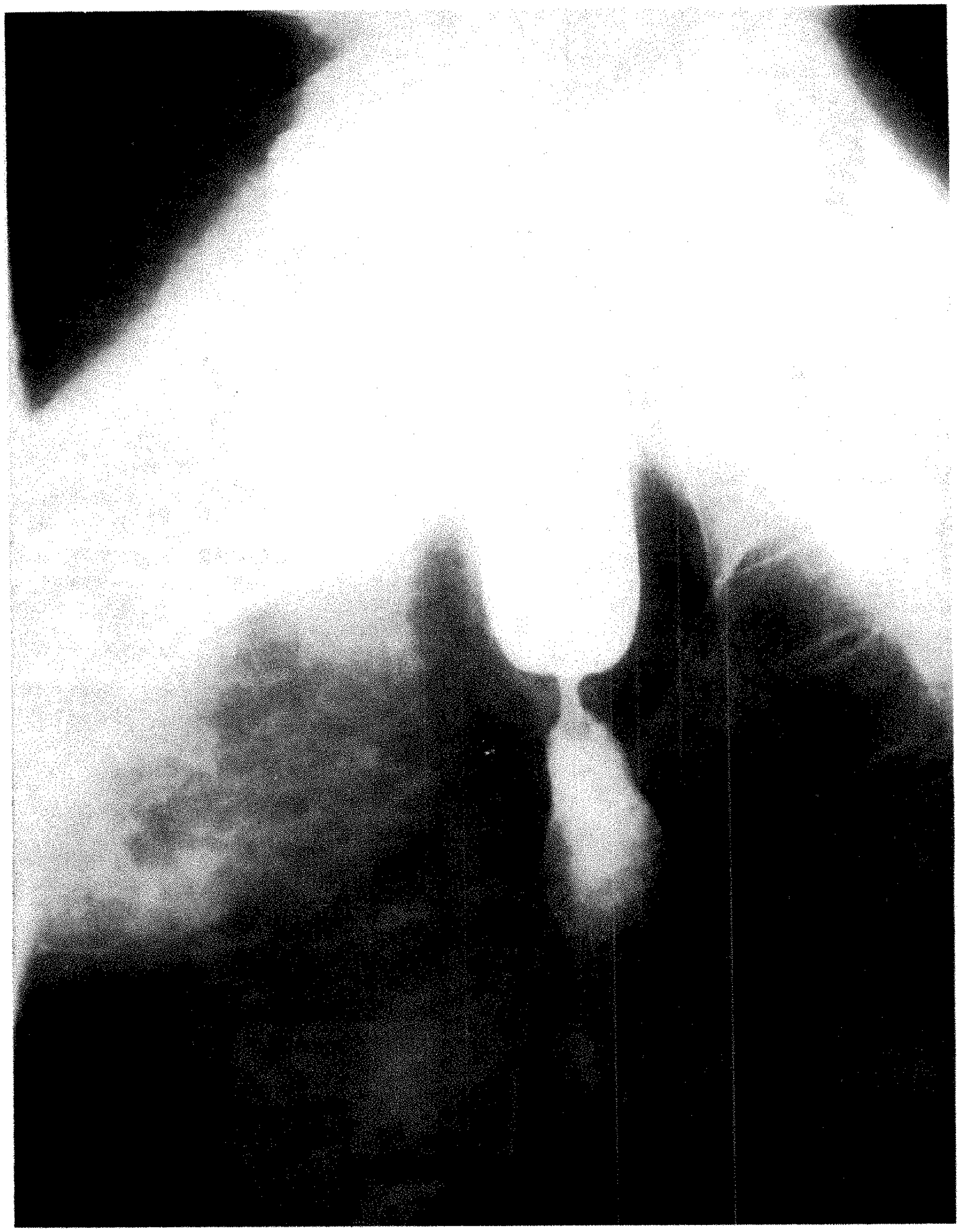

Fig. 1—Esophagram, lateral view. The upper third of the esophagus is dilated, proximal to a short, smooth stricture.

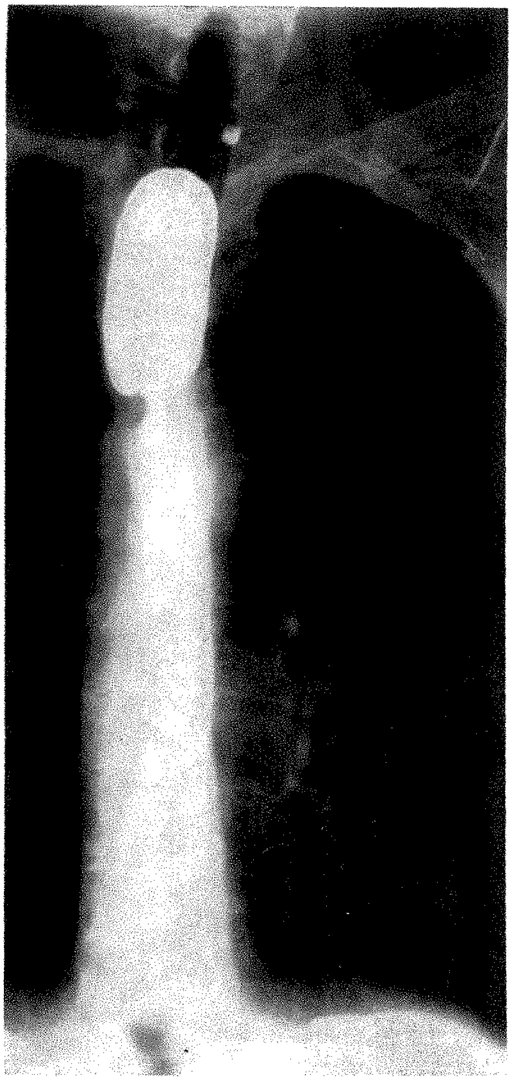

Fig. 2—Same patient as in Figure 1. The stricture is again identified. Incidentally noted is a Zenker's diverticulum.

cent case report described a patient with multiple primary adenocarcinoma in a Barrett's esophagus.[8] The carcinogenesis is unclear, since squamous cell carcinoma is usually associated with alcoholism and chronic irritation. Indeed it is not clear whether adenocarcinoma arises from the site of the Barrett's ulcer, the stricture, or from the otherwise normal gastric epithelium.

Provided that endoscopy with multiple biopsies and brush cytology has revealed no malignancy, treatment is medical. The usual hiatal hernia program and dilatation of the stricture commonly afford relief. Although most authors recommend surgery only as a last resort for distal esophageal stricture, few series compare medical with surgical therapy in mid esophageal stricture due to columnar-lined esophagus. In seven patients with Barrett's esophagus who underwent a modified posterior gastropexy with closure of the hiatus and anchoring of the gastroesophageal junction to the preaortic fascia, the stricture disappeared in five within six to 12 months. In the two other patients, the stricture disappeared in two years.[9]

CASE REPORT

A 64-year old Irishman presented with a four-month history of progressive dysphagia. Although he was able to eat only gruel and liquids, he had not lost weight. There was no history of gastrointestinal bleeding, heartburn or lye ingestion. Past medical history included alcoholism, pulmonary tuberculosis, chronic obstructive pulmonary disease, osteoarthritis and mild hypertension.

Physical examination demonstrated evidence of chronic liver disease but koilonychia and lymphadenopathy were not present.

Esophagram (Figs. 1 and 2) demonstrated a short, smooth stricture of the esophagus at the level of the fifth thoracic vertebra. The proximal esophagus was dilated. A small sliding hiatal hernia was also present.

Endoscopic examination revealed a smoothly stenotic esophageal lumen 3 mm. in diameter at the level of 27 cm. from the incisors. A superficial ulceration encircled

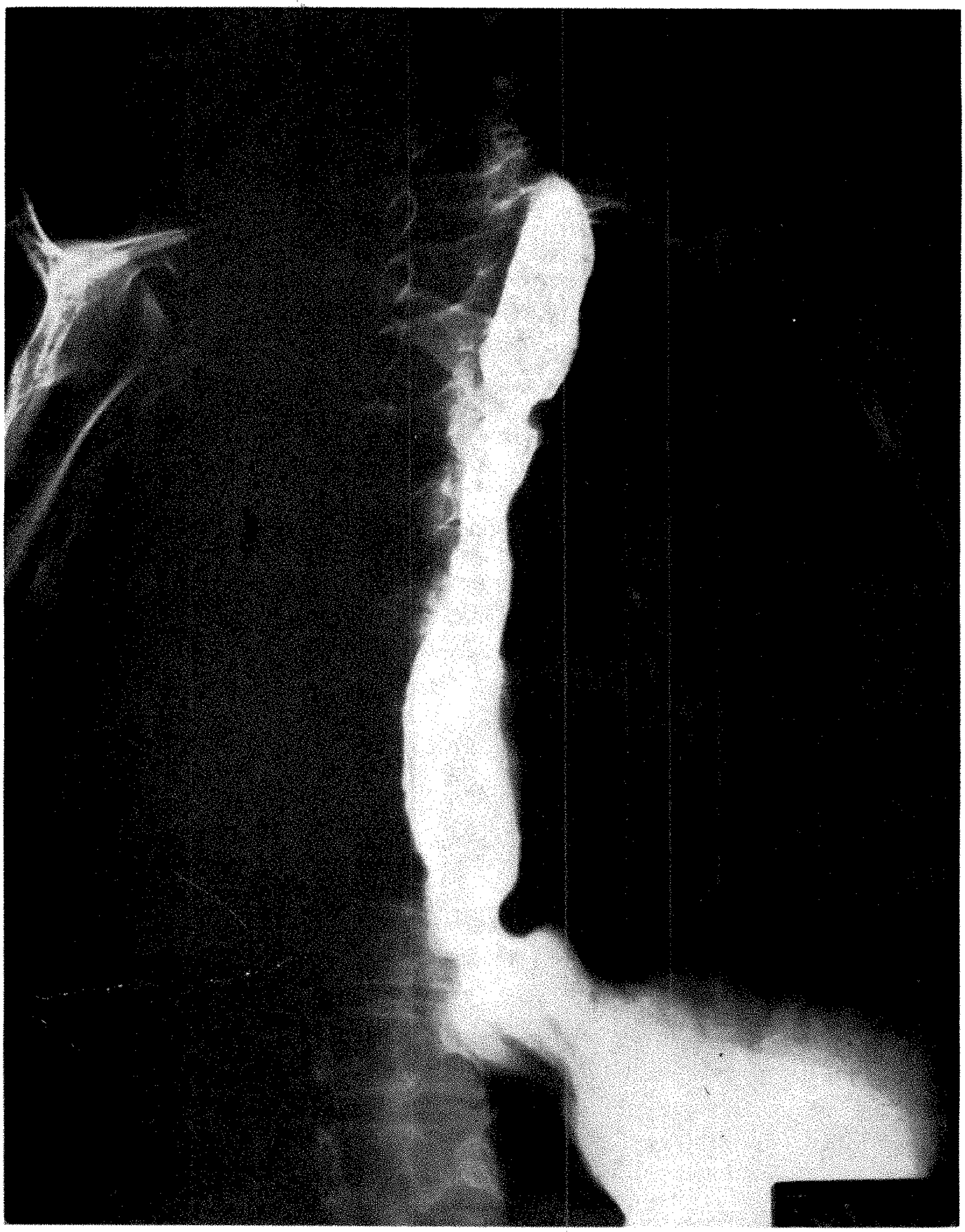

Fig. 3—Second patient (Editors' note). There is a stricture at the level of the arch of the aorta. A hiatal hernia is noted.

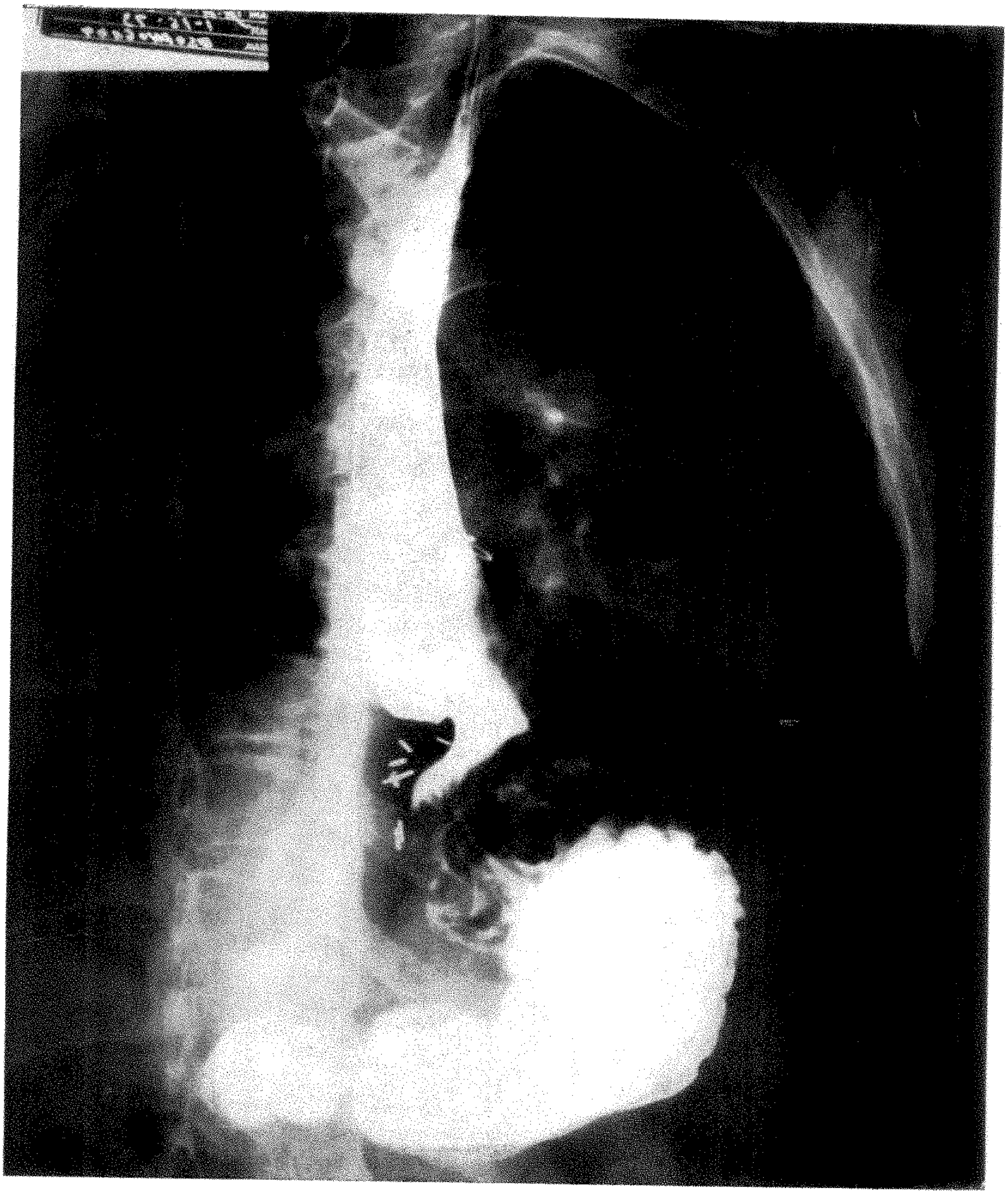

Fig. 4—Same patient as in Figure 3, following hiatal hernia repair. The stricture has disappeared.

the esophagus just proximal to the stricture. The mucosa was diffusely infiltrated and firm. Biopsy of the stricture revealed squamous epithelium with focal areas of hyperplasia in addition to mucosal ulceration and hemorrhage. Adjacent to the squamous epithelium was columnar mucosa containing hyperplastic glands consisting of clear and chief cells. Parietal cells were not seen. There was a moderate amount of edema and inflammation in the gastric-type mucosa. After dilatation, serial biopsies revealed gastric-type epithelium distal to the stricture. No tumor cells were seen on brush cytology or biopsy. The patient's dysphagia diminished after dilatation and conservative therapy.

Editors' note:—We have recently seen another patient with mid esophageal stricture. This 42-year old man had a history of hiatal hernia since age 12. At age 22, a sliding hiatal hernia measuring 6 cm. in length and associated with marked regurgitation was noted on upper gastrointestinal roentgen examination. At age 30 he experienced difficulty in swallowing. Roentgen study demonstrated a stricture at the level of the aortic arch (Fig. 3). Esophagoscopy and biopsy revealed a gastric-lined esophagus. A Belsey hiatal hernia repair was performed. Subsequently there was no regurgitation and the stricture disappeared (Fig. 4). Two years later, the hernia and regurgitation recurred and the stricture was once again demonstrated.

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The Last Page

QUESTIONS IN GASTROENTEROLOGY

MICHAEL RUOFF, M.D., F.A.C.G.[*]
New York, N. Y.

The Last Page appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page,* again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. CONCERNING INFLAMMATORY BOWEL DISEASE (IBD):

A. IBD has similar clinical features and clinical course everywhere in the world.

B. There is a direct correlation between the severity of the bowel disease as demonstrated radiologically and the clinical course.

C. Ulcerative colitis has increased slightly or plateaued and the incidence and prevalence of Crohn's disease has risen rapidly in all parts of the world.

D. The granuloma is specific for Crohn's disease.

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2. FEATURES OF CROHN'S DISEASE INCLUDE:

A. Focal nature of the process.

B. Aphthoid ulcers located over lymphoid aggregates.

C. Right-sided predominance of the inflammation.

D. Depletion of epithelial mucin.

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3. CONCERNING THE COMPLICATIONS OF IBD:

A. Fistula formation is not seen with ulcerative colitis.

B. There are geographic differences in the frequency of carcinoma of the colon-rectum associated with ulcerative colitis.

C. Recurrence after small bowel resection ranges from 85-100%.

D. Recurrences in residual small bowel after total colectomy and ileostomy for Crohn's colitis approximates 35%.

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4. HEPATIC COMPLICATIONS OF IBD INCLUDE:

A. Fatty changes.

B. Pericholangitis.

C. Sclerosing cholangitis.

D. Carcinoma of the bile ducts.

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5. STUDIES OF IBD SHOW THAT:

A. With the possible exception of acute toxic arthritis and *erythema nodosum* colectomy has an inconsistent effect upon the extracolonic manifestations of ulcerative colitis and Crohn's disease.

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B. Colon autoantibodies appear to be secondary reflections of tissue injury.

C. There is no evidence for a primary immune deficiency in the usual case of ulcerative colitis.

D. The *in vitro* cytotoxic effect of circulating lymphocytes for colonic epithelial cells is a unique phenomenon in all IBD patients.

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6. IT HAS BEEN OBSERVED THAT:

A. There is a genetic influence in 50% of IBD patients.

B. Specific genetic markers can be identified in the majority of IBD patients.

C. Approximately 20% of patients with ulcerative colitis and 50% of patients with Crohn's disease require surgery because of complications.

D. Granulomas are not detectable in 30-40% of Crohn's disease tissue.

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7. RANDOMIZED CLINICAL TRIALS EVALUATING TREATMENTS OF GASTRIC ULCER:

A. Support the value of antacids and anticholinergics as the cornerstones of ulcer management.

B. Show that cholestyramine is effective in promoting the healing of gastric ulcers.

C. Show that carbenoxolone is effective in the therapy of gastric ulcers.

D. Have had a significant impact in determining the medical treatment for gastric ulcers.

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8. THE IDEAL ANTACID SHOULD BE:

A. Rapid acting.

B. Able to produce effective neutralizing results when administered in a small dose.

C. Palatable.

D. Harmless.

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9. STUDIES OF IMMUNOGLOBULINS IN LIVER DISEASE REVEAL THAT:

A. Submassive hepatic necrosis is associated with normal or low Ig-G levels.

B. Acute viral hepatitis is associated with raised Ig-G and Ig-M levels.

C. Alcoholic cirrhosis is associated with high Ig-M levels.

D. Primary biliary cirrhosis is associated with elevated Ig-A levels.

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10. A PATIENT WITH ACUTE MESENTERIC ISCHEMIA MAY HAVE:

A. Atrial fibrillation.

B. Severe abdominal pain.

C. Anamnestic data of previous embolism.

D. Bloody stools.

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11. MECONIUM ILEUS EQUIVALENT:

A. Is due to abnormal mucus secretion in patients with cystic fibrosis.

B. May be suspected when plain abdominal x-rays show bubbly material in the right lower abdomen (Newhouse's sign).

C. Can respond to irrigation with 4% n-acetylcysteine.

D. Must be treated surgically.

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12. INTESTINAL BY-PASS FOR MORBID OBESITY:

A. Gradually lowers serum cholesterol and lipids.

B. Makes abnormal glucose tolerance more difficult to control.

C. Employing anastomosis of 35 cm. of jejunum to 20 cm. of ileum and draining the nonfunctioning intestine into the cecum results in almost no problem with electrolyte imbalance.

D. Causes significant deterioration of hepatic function in over 80% of patients.

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13. ANTIBIOTIC-ASSOCIATED COLITIS:

A. Is unique to the use of Clindamycin.

B. Follows oral but not intravenous antibiotic administration.

C. Will respond to steroids which allow the antibiotic to be continued.

D. Produce mucosal changes that are most severe in the more proximal portions of the colon.

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14. PATIENTS WITH SARCOIDOSIS:

A. Have pancreatic involvement in 6% of typical cases at autopsy.

B. Often have clinically important liver disease.

C. With alkaline phosphatase elevation may have either hepatic or pancreatic involvement.

D. Frequently have steatorrhea due to pancreatic insufficiency.

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15. CONGENITAL DUODENAL STENOSIS:

A. Usually involves the proximal duodenum.

B. Has an association with Down's syndrome.

C. Viewed endoscopically gives the appearance of a cervix.

D. May be silent in childhood and become symptomatic in adult life.

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16. COLITIC ARTHRITIS:

A. Most commonly begins insidiously with involvement of multiple small joints of the upper extremities.

B. Occurs in brief self-limiting episodes.

C. Can be very similar to juvenile rheumatoid arthritis if bowel symptoms have not as yet developed.

D. Exacerbations tend to be associated with increased activity of the intestinal disease in adults but not in children or in Crohn's disease.

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17. THE GASTRIC LINED ESOPHAGUS:

A. Can be either a congenital or an acquired abnormality.

B. Is associated with adenocarcinoma.

C. May develop a sharply demarcated, punched-out ulcer (the Barrett's ulcer).

D. May develop a mid esophageal stricture that will disappear after dilatation and repair of an associated hiatal hernia.

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18. ACUTE FULMINANT HEPATIC FAILURE (FHF):

A. May result either from cell necrosis or from organelle dysfunction in living liver cells.

B. Is the sole cause of the encephalopathy in Reye's syndrome.

C. Leads to elevation of all amino acids (from the necrosing liver) with the exception of the branched chain compounds (valine, leucine, isoleucine) which are normal or slightly decreased.

D. May cause encephalopathy by synergistic interaction of methanethiol, NH_4 and fatty acids.

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19. CLINICAL FHF IS SEEN WITH:

A. Acute massive necrosis in viral or toxic hepatitis.

B. Acute steatosis (pregnancy, intravenous tetracycline, Reye's syndrome).

C. Steatonecrosis (alcoholic hepatitis).

D. All of the above.

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20. NEUROCHEMICAL LESIONS IN HEPATIC FAILURE ARE DUE TO:

A. Toxic effects of alpha-ketoglutaramate.

B. NH_3-induced depletion of glutamic and aspartic acids.

C. Inhibition of cytoplasmic-mitochondrial hydrogen transport.

D. Failure of high energy phosphate synthesis.

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21. CEREBRAL EDEMA IN FHF:

A. Is cytotoxic in etiology.

B. Responds poorly to corticosteroid therapy.

C. Is associated with a raised CSF protein.

D. Is a terminal, hypoxic event.

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22. DYSFUNCTION OF OTHER ORGANS IN FHF INCLUDES:

A. Hypotension due to inappropriate systemic vasodilatation.

B. Hyponatremia.

C. Defective hepatic synthesis of coagulation factors with factor VIII levels falling first as it has the shortest half-life.

D. Endotoxemia.

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23. CONCERNING THE NEUROLOGIC ASSESSMENT OF HEPATIC COMA:

A. The presence or absence of oculovestibular reflexes is the best single predictor of outcome.

B. The EEG pattern changes in parallel with the clinical state.

C. The triphasic wave is specific to hepatic coma.

D. Lesions of the brain stem rather than the forebrain cause loss of consciousness.

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24. RECOVERY FROM FHF:

A. Correlates with levels of clotting factors.

B. In patients who can tolerate biopsy is poor if the hepatic volume fraction is less than 35%.

C. Cannot be predicted by the rise in serum alpha fetoprotein which is related to the duration of survival but does not necessarily imply ultimate recovery.

D. May be predicted by a test of galactose elimination capacity that measures the functional hepatic mass.

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25. TREATMENT OF FHF SHOULD INCLUDE:

A. Anticerebral edema therapy with intravenous Mannitol in Reye's syndrome.

B. Vigorous correction of hypocapnia.

C. Control of delirium if necessary with oral Oxazepam or intravenous Valium.

D. Oxygen administration.

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26. PROBLEMS OF THERAPY IN FHF INCLUDE:

A. Steroids increasing the plasma urea concentration, body urea pool and synthetic rate of urea.

B. Oxygen administration by PEEP having adverse effects on cerebral and hepatic circulation.

C. Sedation depressing respiration and blood pressure.

D. Coagulation factor concentrates increasing the tendency to intravascular concentration.

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27. IN ACUTE FULMINANT HEPATIC FAILURE:

A. Eighty to ninety per cent of such patients whose disease has progressed to stage IV coma die.

B. Controlled studies with hepatic assist charcoal hemoperfusion devices have proven the effectiveness of this procedure.

C. Potential cerebrotoxins include increased aromatic and reduced branched amino acids and false neurotransmitters like octopamine.

D. Falling levels of prothrombin and complement are useful markers of the fulminant nature of hepatocellular failure.

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

Radiology of the Alimentary Tract in Infants and Children, Vol. 10, 2nd edition: by Edward B. Singleton, M.D., Milton L. Wagner, M.D. and Robert V. Dutton, M.D. 461 pages, illustrated. W. B. Saunders Co., Philadelphia, PA, 1977. Price $26.00.

Drs. Edward B. Singleton, Milton L. Wagner, and Robert V. Dutton have written a comprehensive and authoritative text entitled *Radiology of the Alimentary Tract in Infants and Children*. This second edition, the tenth volume in Saunders' Monographs in Clinical Radiology, provides a clarified approach to the examination of the gastrointestinal tract in the pediatric age group. It is well illustrated with excellently reproduced radiographs throughout. The bibliography, however, suffers from age as in all textbooks but most of the references cited have become classics.

The group from the Texas Children's Hospital and the Texas Heart Institute authoritatively update and compile the accumulated knowledge concerning pediatric alimentary tract radiology. The textbook successfully fills a need for the pediatrician, general pediatric surgeon, pediatric gastroenterologist and radiologist and should be a welcome addition to the libraries of these practitioners.

M. A. Bleicher, M.D., F.A.C.G.

Basic Surgery: by John A. McCredie, M.B. 660 pages, illustrated. Macmillan Publishing Co., Inc., New York, NY, 1977. Price $15.95.

McCredie's *Basic Surgery* is a soft-covered unpretentious text which is just Jim Dandy. It is simple, concise, readable and just what the doctor ordered for our hassled students, interns and residents. The classical texts now in use have been revised and expanded to a point which renders them too formidable for the student. Basic Surgery *can* be read during a clerkship.

The 35 chapters are divided into four units: 1. Basic considerations stressing basic medical science or the physiology of disease states as related to surgical disease. 2. Total care of the surgical patient reminding the young surgeon that he is a physician as well as a cutter. 3. Principles of general surgery which covers the most important surgical disorders of the viscera. 4. Principles of specialty surgery treating orthopedics, cardiopulmonary, peripheral vascular, urologic, reconstructive and plastic, neurosurgical and pediatric surgery.

A good buy for the money.

David A. Dreiling, M.D., F.A.C.G.

Guide To Ostomy Nursing Care: by Joanne M. Mahoney. 246 pages, illustrated. Little, Brown and Company, Boston, MA, 1976. Price $6.95.

This is an absolutely superb manual which covers in detail all aspects of the care of the patient with an "ostomy". It is obviously the result of a detailed consideration of the normal care of and problems related to, various types of abdominal stomas, by a qualified enterostomal therapist. Practically every important question which arises during the course of management of such patients is answered simply, clearly and succinctly.

This book is a must for all nursing staff who deal with stomas, for nonspecialized nurses who care for stomas, for the "otomate" who would like intelligent answers to his or her questions. It will also be of value to surgeons and gastroenterologists who have patients with inflammatory bowel disease, or colonic cancer requiring the creation of an ileostomy or a colostomy.

Adrian J. Greenstein, M.D., F.A.C.G.

Gastroenterologie: by P. H. Clodi. 203 pages, illustrated. Springer-Verlag, Berlin, Germany, 1976. Price $13.00.

This compendium written in German, is designed as a quick reference booklet for the practicing physician. The clinical manifestations of gastrointestinal syndromes are briefly outlined without much attention or discussion of the pathogenesis. A useful booklet for those who can read German.

Demetrius Pertsemlidis, M.D., F.A.C.G.

Gastroenterology, Vol. III, 3rd edition: edited by Henry L. Bockus, M.D., F.A.C.G. (Hon.). 1,211 pages, illustrated. W. B. Saunders Co. Philadelphia, PA, 1976. Price $38.00.

Gastroenterology, Vol. IV, 3rd edition: edited by Henry L. Bockus, M.D., F.A.C.G. (Hon.). 795 pages, illustrated. W. B. Saunders Co. Philadelphia, PA, 1976. Price $34.00.

Bockus Vol. III and Vol. IV are here completing the Magnum Opus. Vol. III treats the liver, gallbladder, bile ducts and pancreas. Vol. IV is a catchall for peritoneum, parasites, etc. There is no doubt that the four volumes are the most authoritative text but I must say something has been lost in the expansion and internationalization. To take the section on the pancreas, I found it morcelated and repetitious. In an equivalent space, a more cohesive and meaningful text has been fashioned by several others. When books get too large, they are admired and not read. When reference in detail and depth is required it is better found in a monograph.

David A. Dreiling, M.D., F.A.C.G.

Topics in Gastroenterology, #4: edited by S. C. Truelove, M.D. and J. A. Ritchie. 384 pages, illustrated. J. B. Lippincott Co., Philadelphia, PA, 1977. Price $39.50.

Topics in Gastroenterology is the fourth in a series of edited lectures of an Oxford postgraduate course in gastroenterology. This volume covers viral hepatitis, reflux esophagitis and hiatal hernia, radioisotopes in gastroenterology and miscellaneous subjects including CAT, H_2 receptor antagonists, carbenoxolone, etc. The radioisotope section is excellent, as is the miscellaneous which is timely and germane.

David A. Dreiling, M.D., F.A.C.G.

Gastrointestinal Emergencies: edited by Franz R. Barany, M.D. and Aldo Torsoli, M.D. 428 pages, illustrated. Pergamon Press Inc., Elmsford, NY, 1977. Price $30.00.

Gastrointestinal Emergencies is the compilation of the proceedings of an international symposium held in 1975. The papers have been appended to each other with marked variations in style and print, of interest to the participants.

David A. Dreiling, M.D., F.A.C.G.

The Acute Abdomen, an Approach to Diagnosis and Management, 2nd edition: by Thomas W. Botsford, M.D. and Richard E. Wilson, M.D. 325 pages, illustrated. W. B. Saunders Co., Philadelphia, PA, 1977. Price $8.50.

This is a very useful book for all those interested in the acute abdomen. Physicians and surgeons as well as medical students will benefit from the concise and accurate presentation of all clinical syndromes related to abdominal crises. The newer diagnostic methods such as abdominal sonography and angiography have been included in this compendium to make it more useful than previous texts on the acute abdomen.

Demetrius Pertsemlidis, M.D., F.A.C.G.

Recent Advances in Gastroenterology-#3: edited by Ian A. D. Bouchier, M.D. 338 pages. illustrated. Churchill Livingstone, New York, NY, 1976. Price $32.50.

This is one of Dr. Bouchier's attempt to keep us up-to-date in the mushrooming of knowledge that gastroenterology is experiencing. Like Alice-in-Wonderland he is running very hard. The contributors are mainly British. The articles are very good and cover among the following: Physiology of the gastroesophageal junction and hiatus hernia; Fat absorption; Hormone secreting tumors of the gastrointestinal tract; The use and abuses of laxatives; Alcohol and the gastrointestinal tract; Endoscopic cannulation of the papilla of Vater; Clinical aspects of bile acid metabolism, Shunts for hepatic disease; Liver Disease in infants and children; and Cystic fibrosis of the pancreas. If you recognize your weaknesses among these, go to it.

David A. Dreiling, M.D., F.A.C.G.

Surgical Techniques Illustrated. Vol. 1, No. 4. Aneurysmectomy of the Abdominal Aorta, Radical Axillary Dissection: Edited by Ronald A. Malt, M.D. 90 pages, illustrated. Little, Brown and Company, Boston, MA, 1976. Subscription $68.00/yr.

Surgical Techniques Illustrated. Vol. 2, No. 1. Abdominoperineal Resection, Thyroidectomy: edited by Ronald A. Malt, M.D. 90 pages, illustrated. Little, Brown and Company, Boston, MA, 1977. Subscription $68.00/yr.

Surgical Techniques Illustrated. Vol. 2, No. 2. Anterior Resection of the Rectum, Sphincter-Saving Rectal Resections: edited by Ronald A. Malt, M.D. 90 pages, illustrated. Little, Brown and Company, Boston, MA, 1977. Subscription $68.00/yr.

The folios of Little, Brown's *Surgical Techniques Illustrated* present the following operations: Resection of abdominal aortic aneurysm, radical axillary dissection, abdominal perineal resection, thyroidectomy, anterior resection of the rectum and sphincter saving rectal resections. The format remains a brief clinical consideration, numerous stepwise illustrations of the procedure, with pertinent and personalized comment by the outstanding surgeon describing his technic. The educational value to the resident is clear, the different and many roads to Rome should be eye-opening but why, oh why must there be such diversity of art style: some good, some so-so, and some downright poor!

David A. Dreiling, M.D., F.A.C.G.

Immunology of the Gut: Ciba Foundation Symposium 46 (new series) 376 pages, illustrated. Excerpta Medica, Amsterdam, Holland, 1977. Price $28.75.

Ciba Foundation Symposium #46—*Immunology of the Gut* is a superb update of our knowledge in this area and hence of great value to many disciplines including pathology, pediatrics, gastroenterology as well as oncology. It is well worth scrutinizing.

David A. Dreiling, M.D., F.A.C.G.

The High-Fiber Cookbook: by Mabel Cavaiani. 286 pages. Henry Regnery Company, Chicago, IL, 1977. Price $9.95.

Increasing dietary fiber content, especially in light of current research in diverticulitis and colon cancer, is a concern that could be met more satisfactorily than it is in this book by Mabel Cavaiani, a home economist and registered dietician. Of the approximately 260 pages of recipes, over half (150) are devoted to breads and desserts, which seems disproportionate, although it may accurately reflect American eating habits. The recipes are not concerned with dietary restrictions and would not be suitable for those on low sodium, low cholesterol or sugarless diets. Further, the number of processed foods and brand-name ingredients in many of the recipes underscores the author's reliance on contributions from commercial test kitchens (Checkerboard, Swift & Co., Quaker Oats) whose main concern is product promotion.

As an alternative, the Department of Agriculture handbook referenced at the end of this book (No. 8, "Composition of Foods: Raw, Processed, Prepared") can be obtained from the U.S. Government Printing Office for $2.25 (over $7.00 less than this cookbook). The fiber content information in the handbook could be incorporated into anyone's existing menu plans and recipes, meeting individual dietary tastes and needs.

Demetrius Pertsemlidis, M.D., F.A.C.G.

Annual Review of Medicine: Selected Topics in the Clinical Sciences, Vol. 28: edited by William P. Creger. 537 pages, illustrated. Annual Reviews Inc. Palo Alto, CA, 1977. Price $17.00.

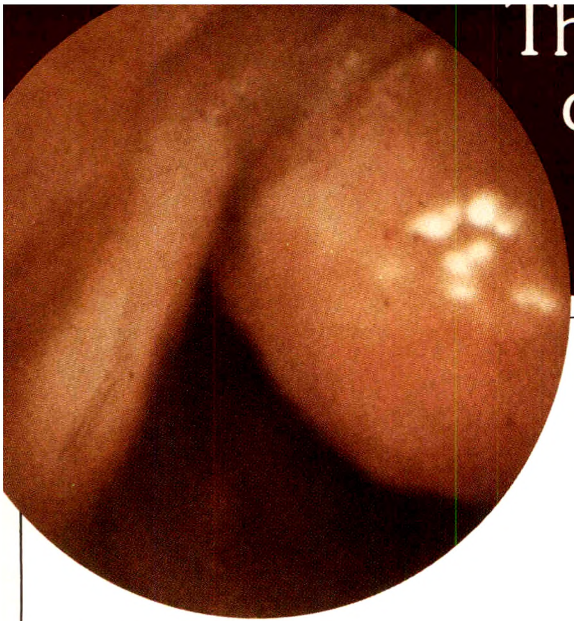
The *Annual Review of Medicine* presents, as it has in the past, a number of selected topics intended to update medical information. Volume 28 has some 42 sections grouped under the following: Allergy and immunology, cardiovascular, dermatology, endocrinology and metabolism, gastrointestinal tract, hematology, infection, kidneys and urinary system, nutrition, ophthalmology, neoplasia, psychiatry, respiratory system and miscellaneous. The invited reviews furnish, of course, an excellent basis for update of medical information to the practitioner who has not the time to read many journals as well as for the student preparing for Board examinations.

David A. Dreiling, M.D., F.A.C.G.

Surgical Techniques Illustrated, Vol. 2, No. 3, Thoracic Sympathectomy: edited by Ronald A. Malt, M.D. 83 pages, illustrated. Little Brown and Company, Boston, MA, 1977. Subscription $68.00/yr.

This volume of surgical technics illustrated is devoted to sympathectomy and vagisection. Four technics of thoracic sympathectomy are presented. Selective and proximal gastric vagotomy complete the volume. The technic of operation is clear in all instances. The illustrations and annotations are good. I thought Goligher's highly selective vagotomy was best done.

David A. Dreiling, M.D., F.A.C.G.



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Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

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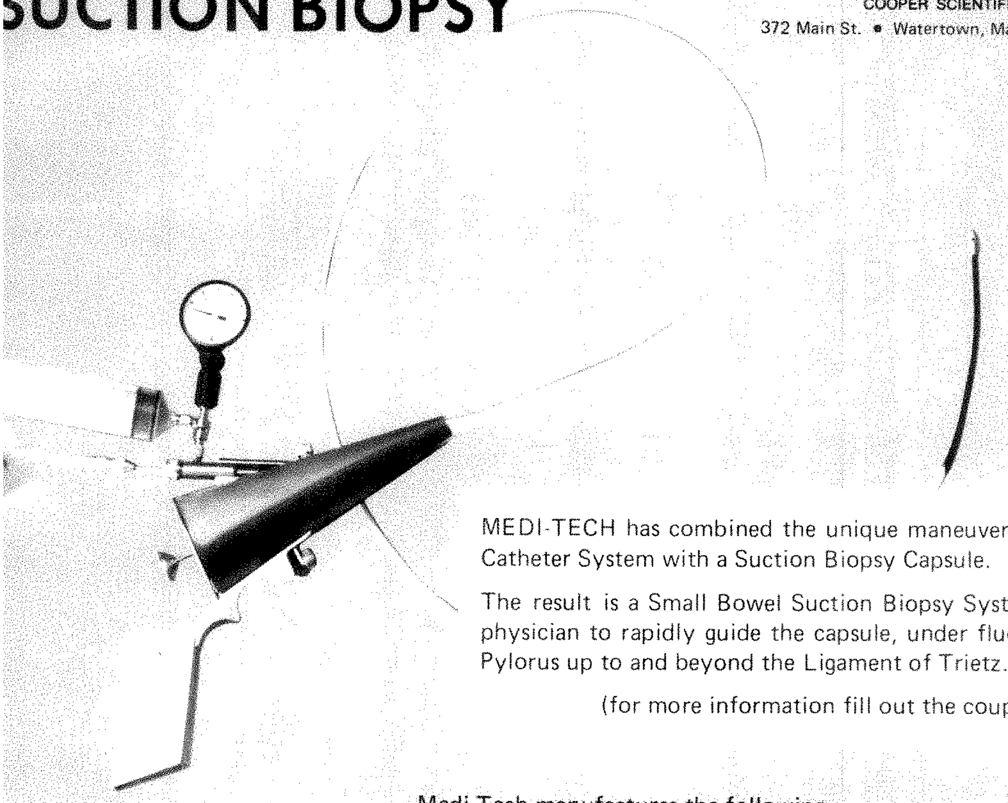

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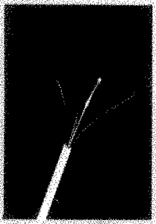
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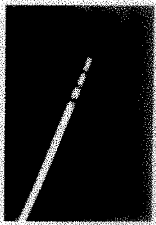
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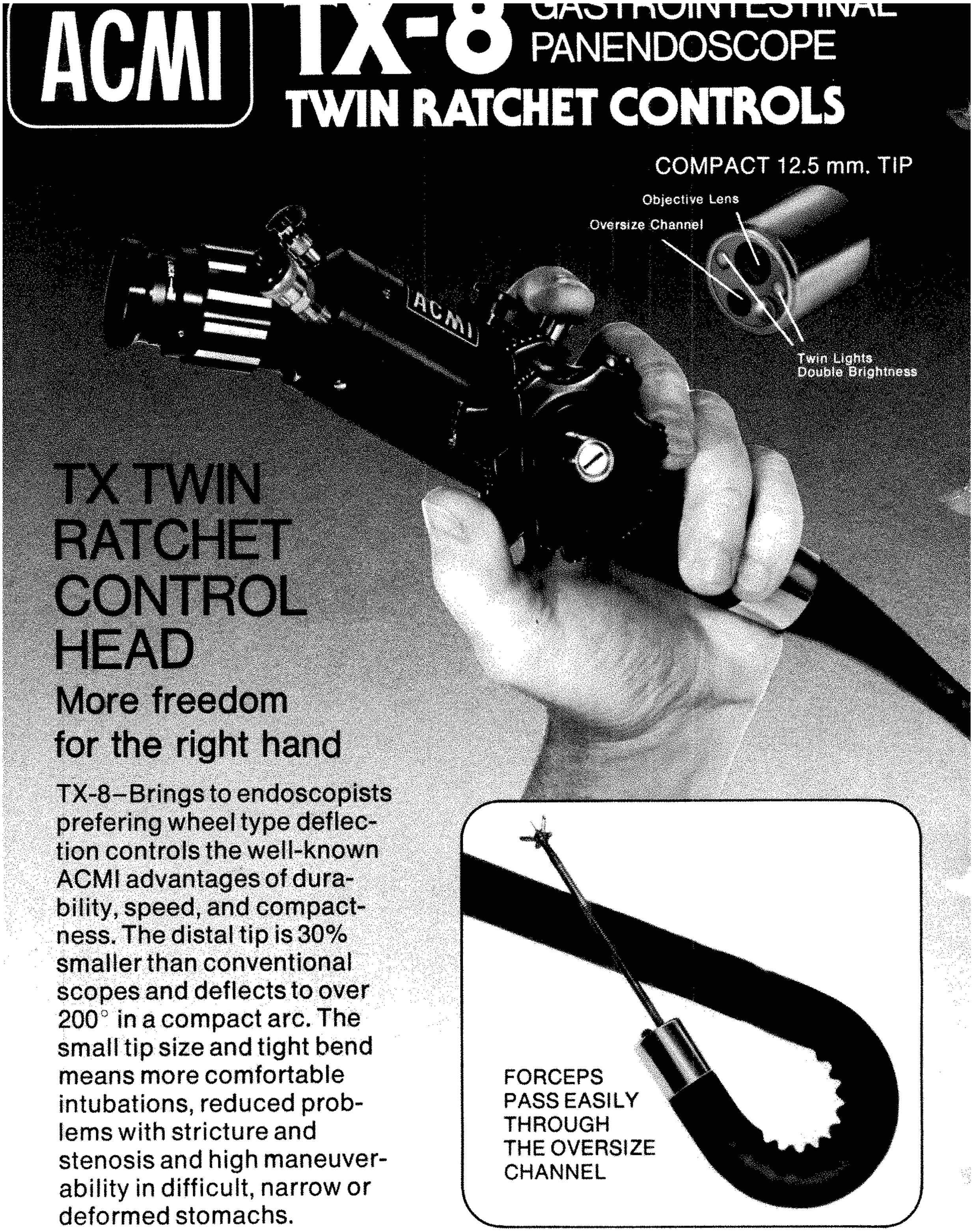
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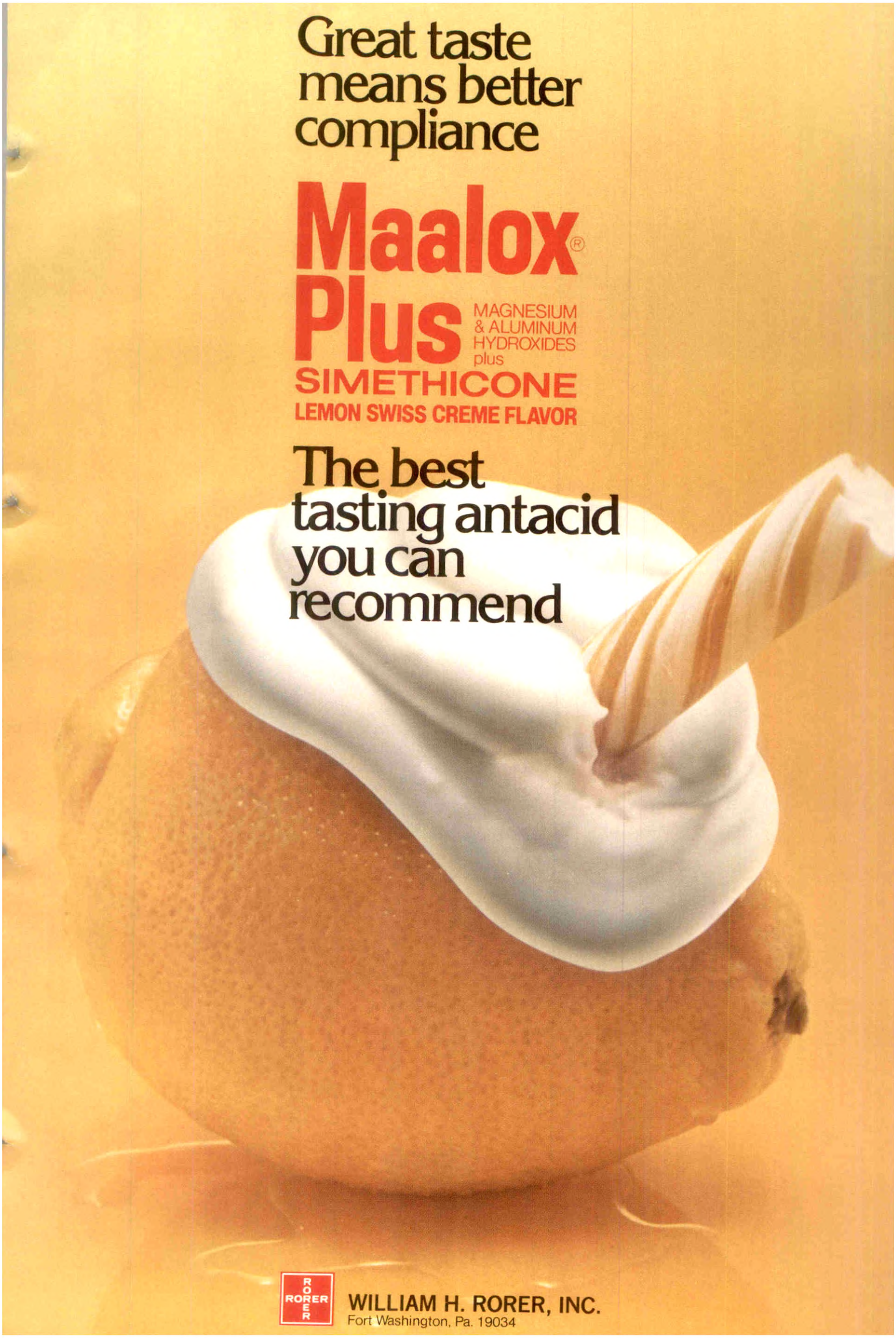

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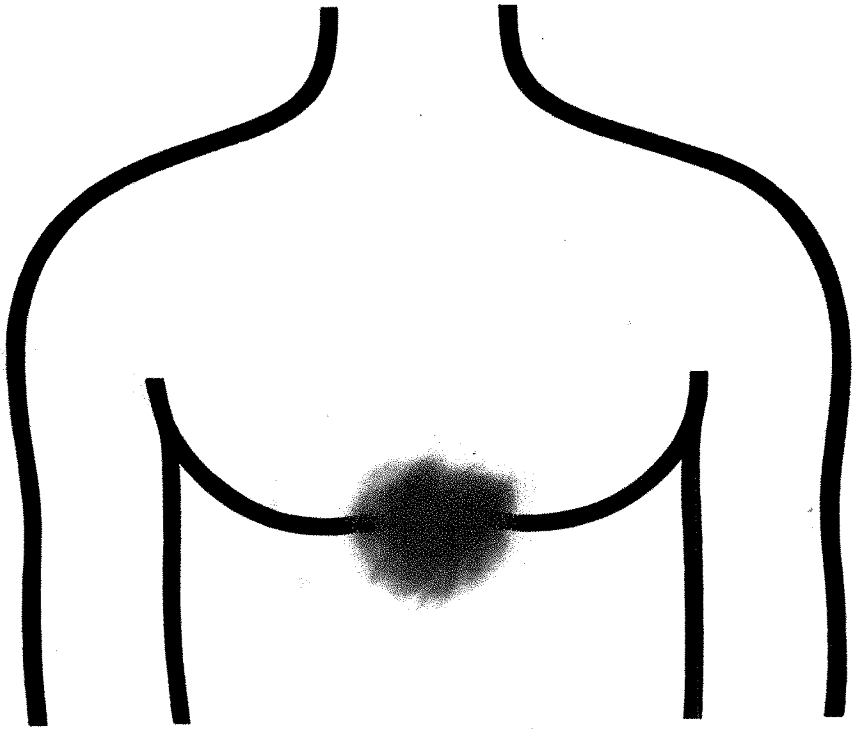

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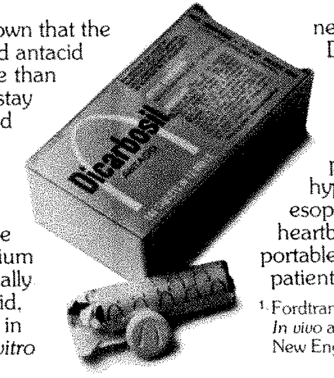

[1] Fordtran, J.S.; Morawski, B.A., and Richardson, C.T.: *In vivo* and *in vitro* evaluation of liquid antacids. New Eng. J. Med. 288:923-28, 1973.

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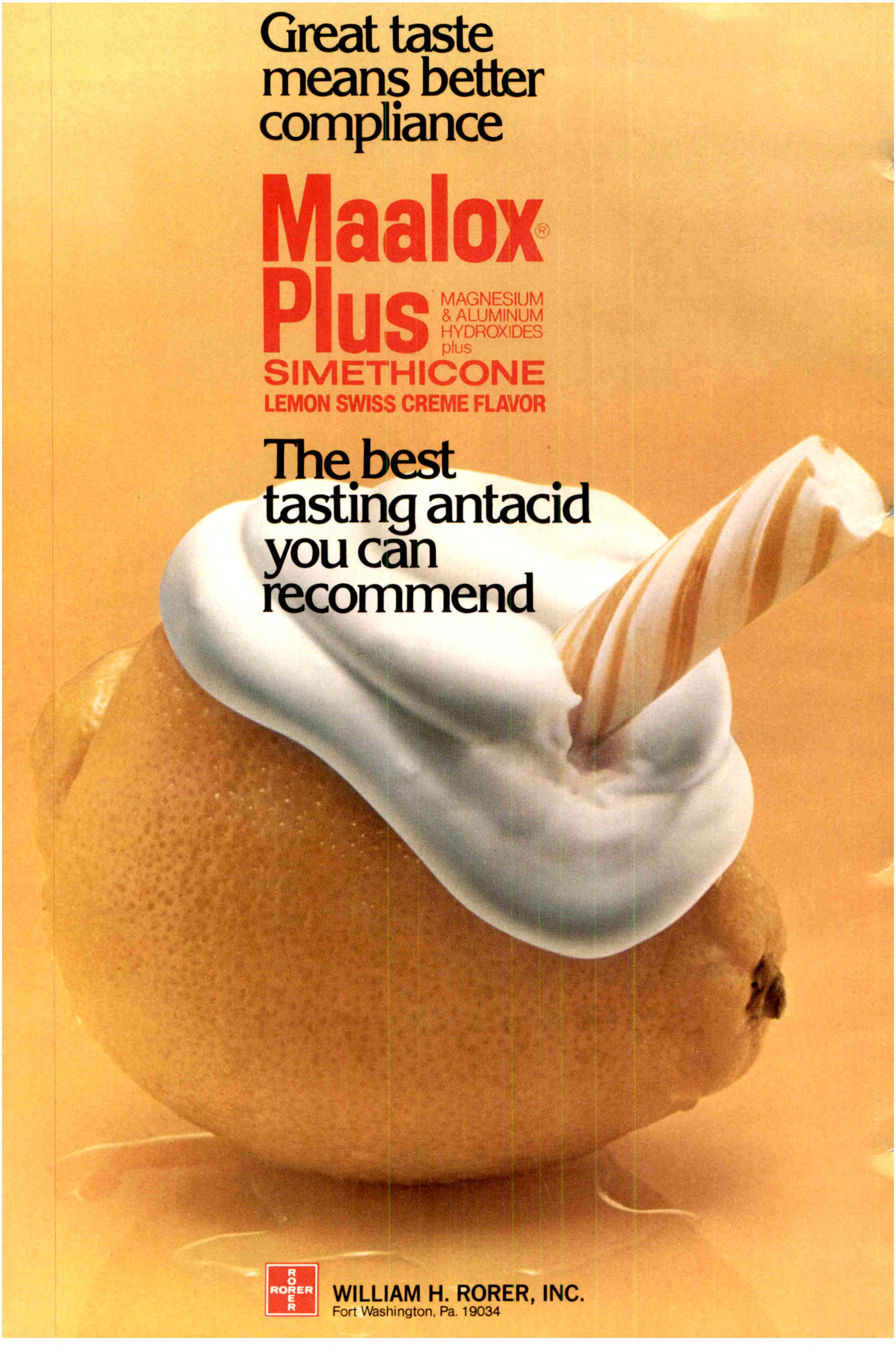

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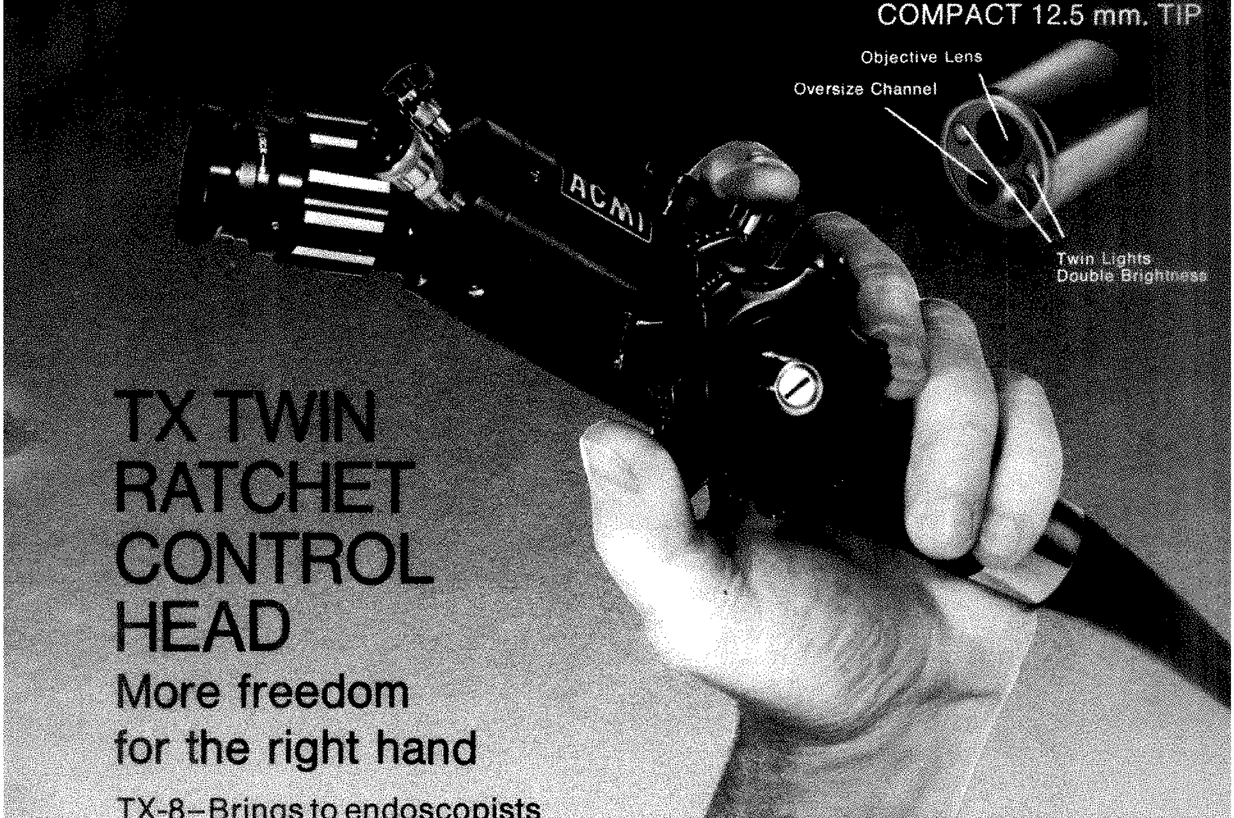

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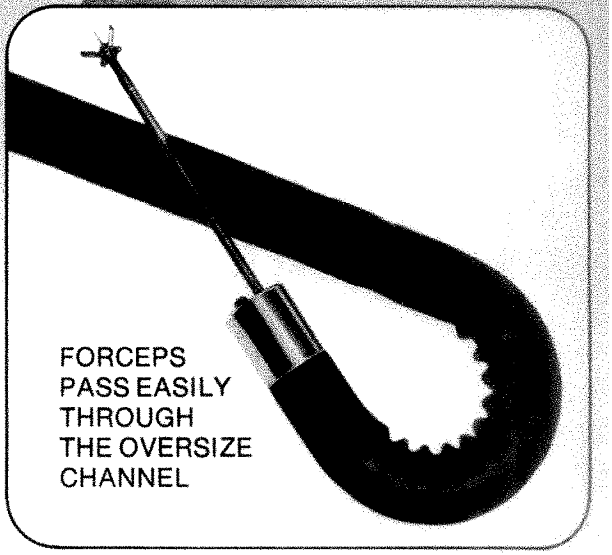
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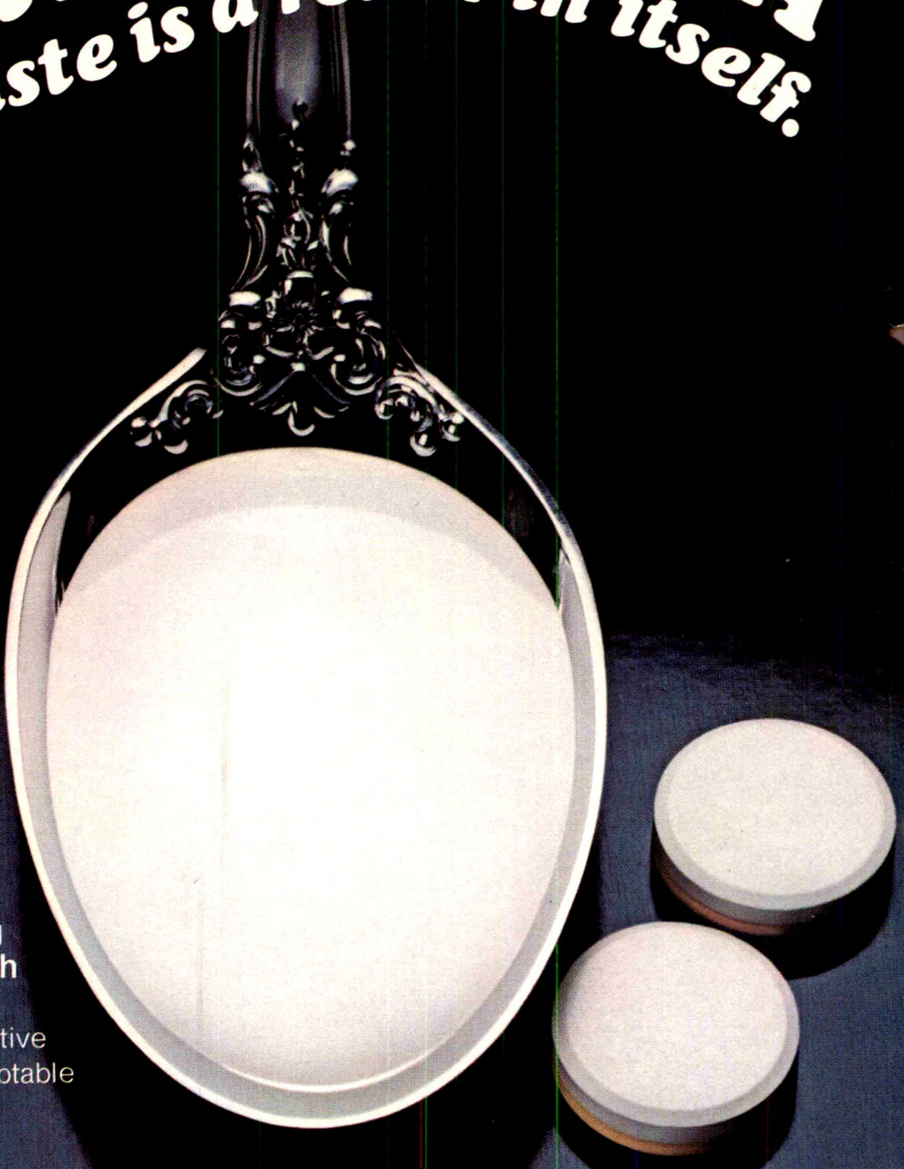

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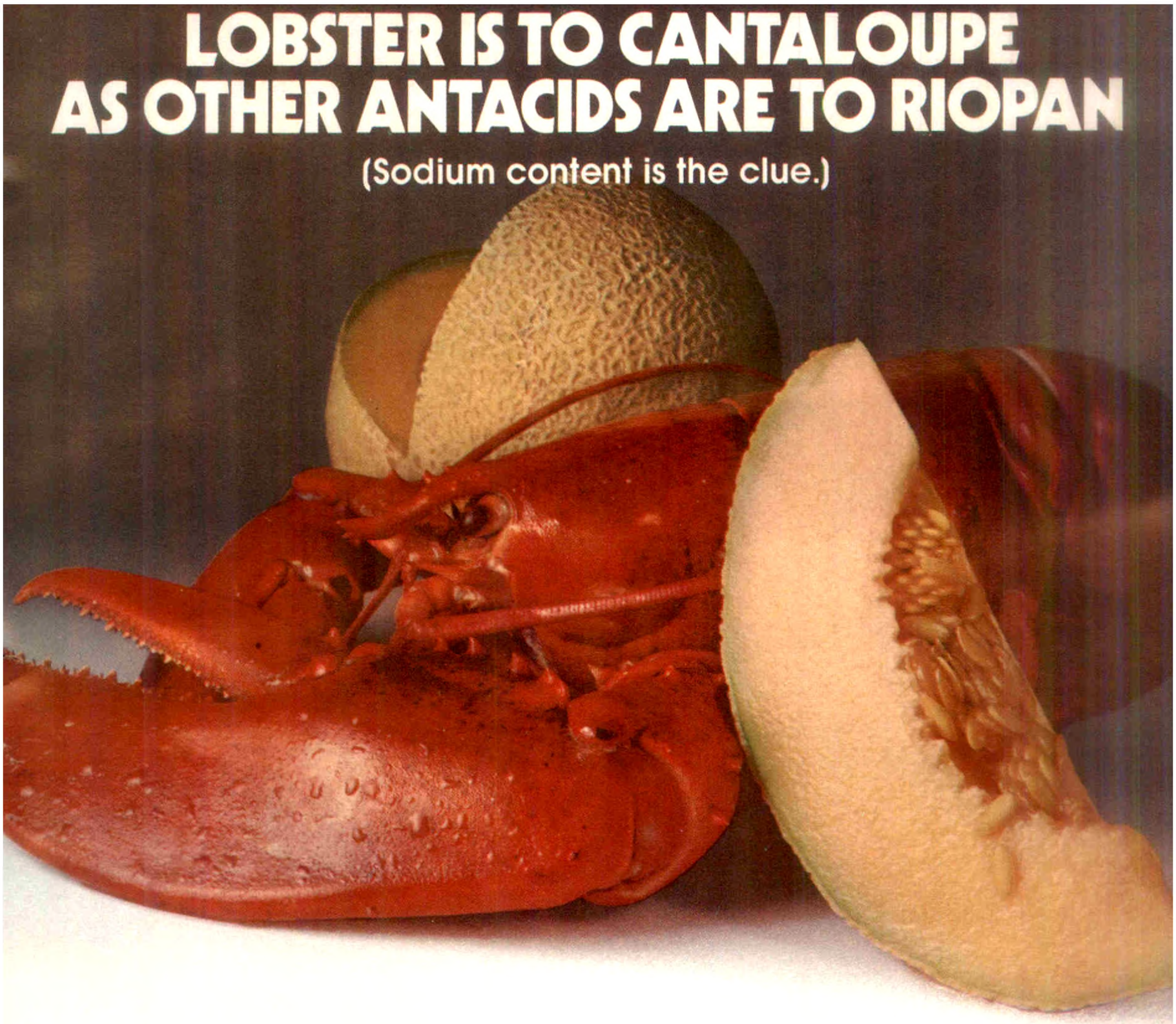
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1. Davidson, C.S., et al.: Sodium-Restricted Diets, Publication 325, Division of Biology and Agriculture, National Research Council, July 1954, pp. 40, 44.
2. Penna, R.P., et al. (eds.): Handbook of Nonprescription Drugs, Washington, D.C., American Pharm. Assn., Ed. 5, 1977, pp. 13-17.
3. Penna, R.P.: Antacids, in Handbook of Nonprescription Drugs, Washington, D.C., American Pharm. Assn., 1973 Ed., pp. 12, 14.
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References to an article with *3 or less authors:*

1. Robinson AS, Sommer DA, Levinson M: Transfiberscopic removal of esophageal polyps. Am J Gastroenterol 61:297-300, 1974.

References to an article with *more than 3 authors:*

2. Starzl TE, Lee IY, Porter KA, et al: The influence of portal blood upon lipid metabolism in normal and diabetic dogs and baboons. Surg Gynecol Obstet 140:381-388, 1975.

Reference to a book:

3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

Reference to an article in a book:

4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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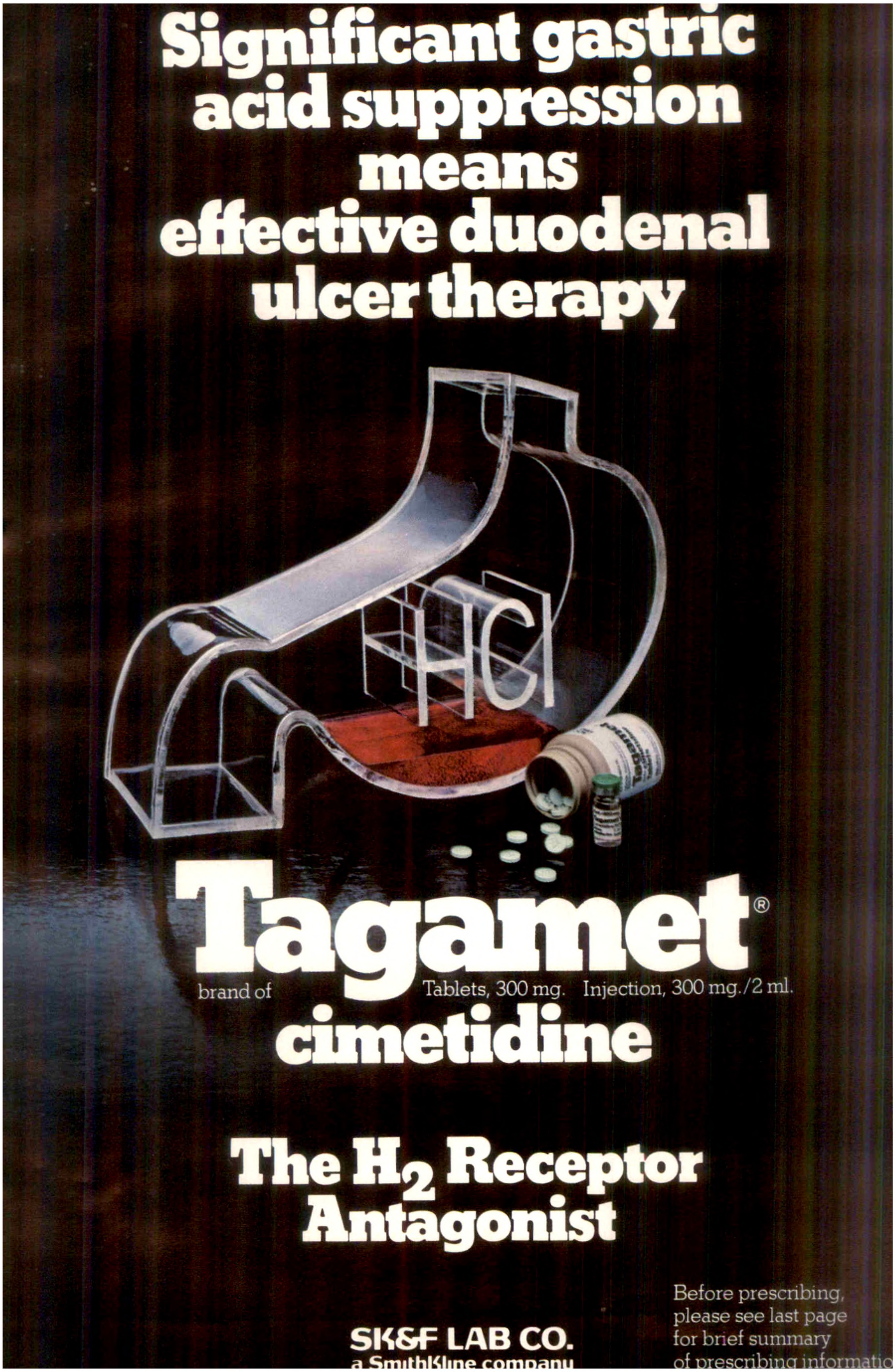

Significant gastric acid suppression means effective duodenal ulcer therapy

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Tablets, 300 mg. Injection, 300 mg./2 ml.
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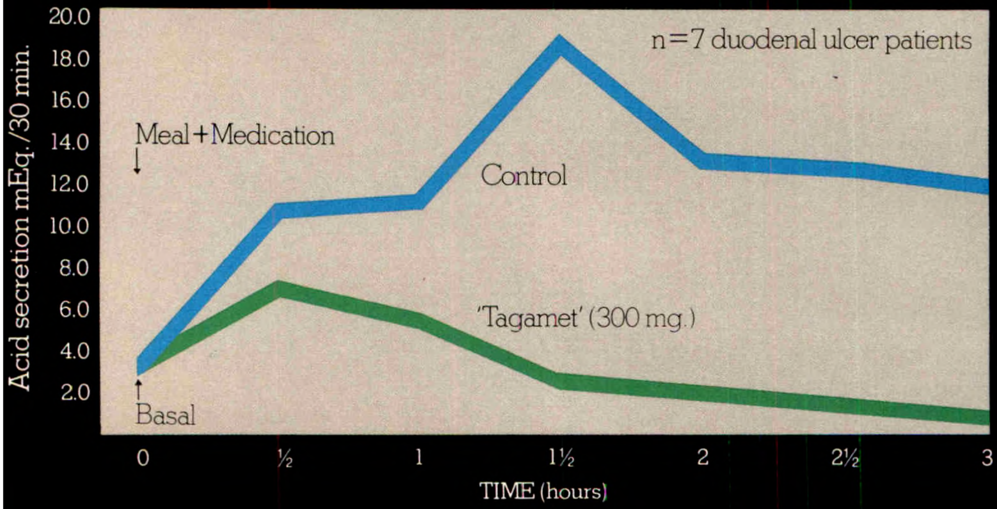
'Tagamet' inhibited meal-stimulated acid secretion by more than 70% over 3 hours.[1]



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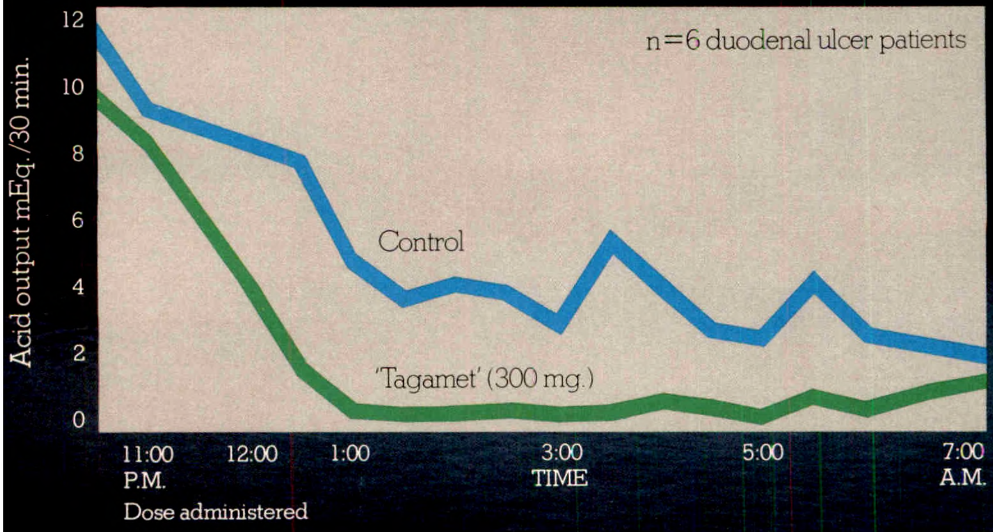

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References

1. Richardson, C.T., et al. Gastroenterology 71 (1): 19-23 (July) 1976.
2. Longstreth, G.F., et al. New England J. Med. 294:801-804 (Apr.) 1976.

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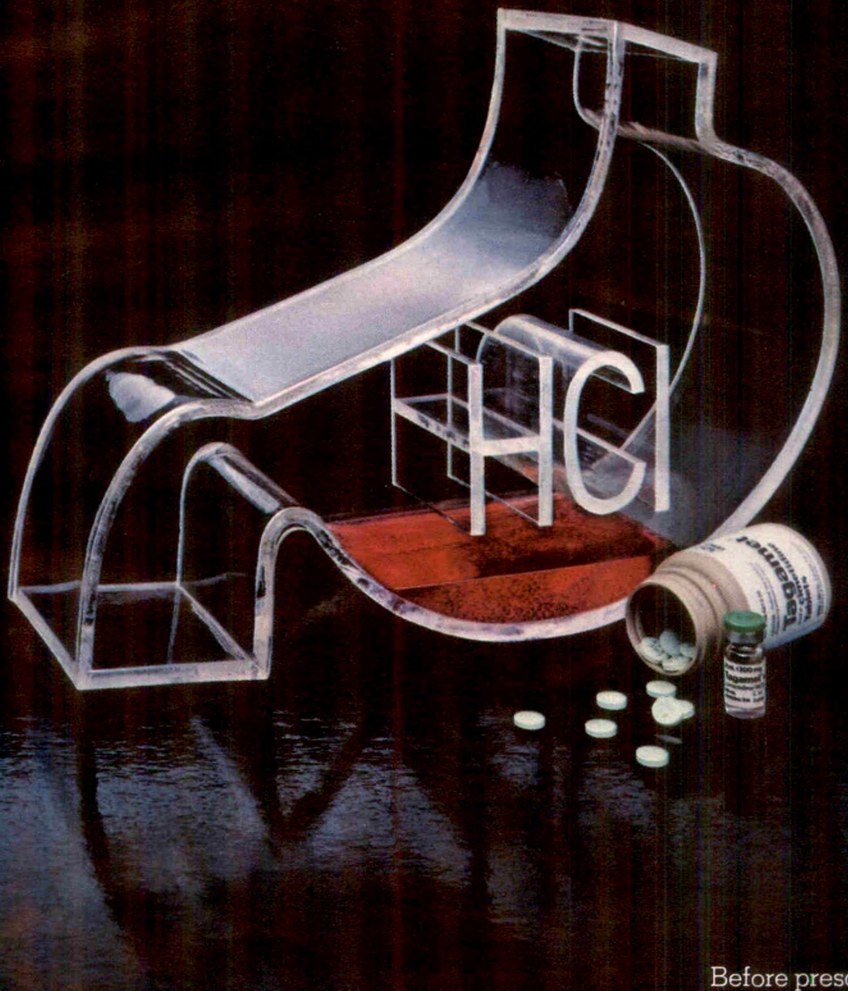

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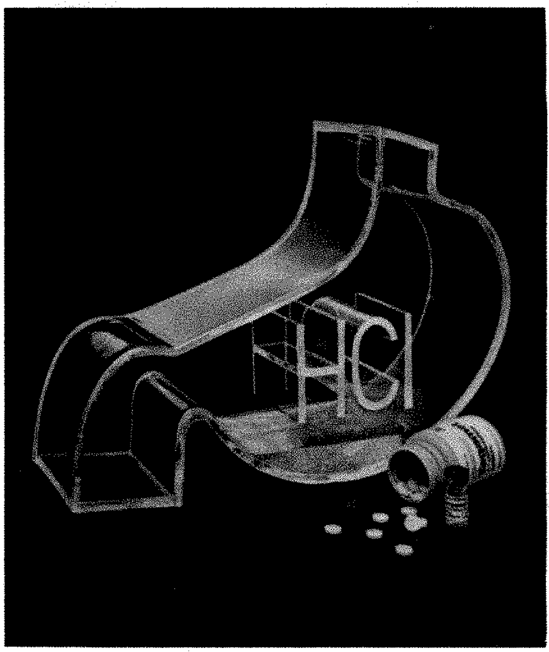

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In *Duodenal Ulcer*, the recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been demonstrated by endoscopic examination.

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Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of neutropenia have been reported, but no causal relationship could be established. Small, regularly observed, reversible increases in plasma creatinine and some increases in serum transaminase have been reported.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials in packages of 10.

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Cortenema®
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COMPOSITION: Each 60 ml. unit contains Hydrocortisone, 100 mg. in an aqueous solution of carboxypolymethylene, polysorbate 80, and methylparaben, 0.18% as a preservative.
INDICATIONS: Adjunctive therapy in ulcerative colitis; especially distal ulcerative proctitis, proctosigmoiditis, left-sided colitis; proved useful also in some cases involving transverse and ascending colons.
CONTRAINDICATIONS: Systemic fungal infections; recent ileocolostomy.
WARNINGS: In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.

Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
ADVERSE REACTIONS: Local pain or burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:

Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
HOW SUPPLIED: Single-dose 60-cc. bottles, in packages of 1 or 7, with instructions for patients.

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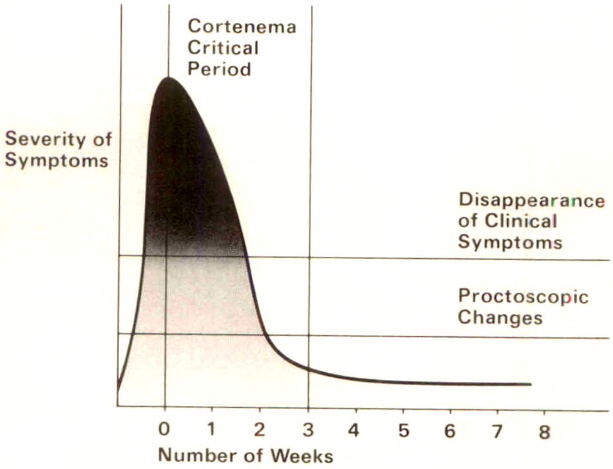

Once a diagnosis is established, Cortenema often is the only medication required for treatment of mild to moderate distal ulcerative colitis, characterized by rectal bleeding, stool abnormality (diarrhea or constipation), and diffuse mucosal ulceration and friability limited to the rectum or rectosigmoid colon.

Progress of signs and symptoms

Inflammation, bleeding and tenesmus usually start to subside within three to five days. Sigmoidoscopic examination after two or three weeks will reveal extent of mucosal improvement and direct subsequent therapy. (Severe cases may require up to three months Cortenema treatment followed by gradually reduced doses until discontinuation.)

Patient convenience and economy

Cortenema is unit-dosed, ready to administer, disposable. Available in packages of one or seven.

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Hydrocortisone enema therapy provides relief of symptoms and mucosal inflammation with minimal concern for steroid side effects. About 30%-50% absorption may occur, but with only transient adrenal suppression reported. Therapy is economical for the patient. The usual three week course costs far less than even one day of hospitalized treatment.

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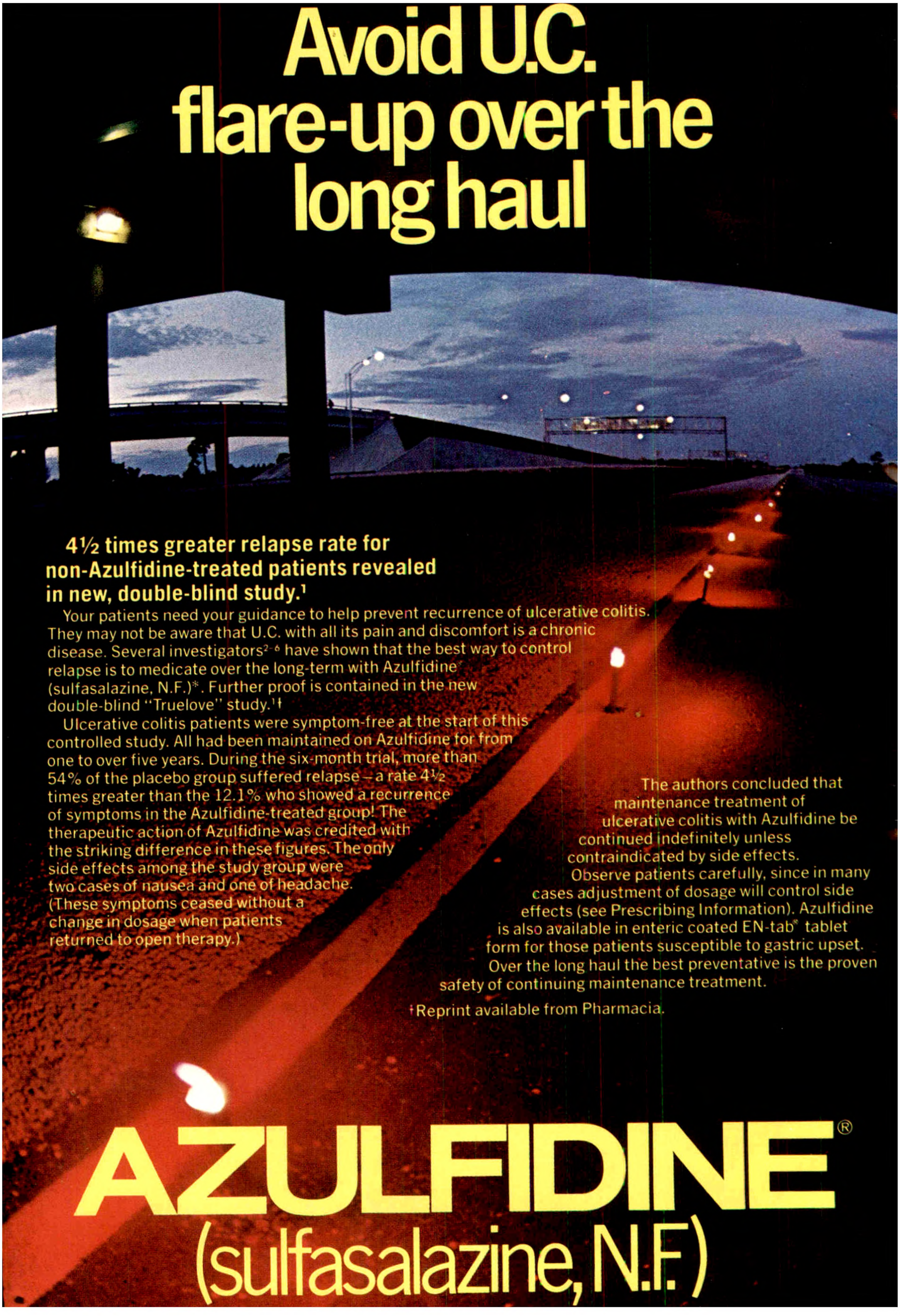
Avoid U.C. flare-up over the long haul



4½ times greater relapse rate for non-Azulfidine-treated patients revealed in new, double-blind study.[1]

Your patients need your guidance to help prevent recurrence of ulcerative colitis. They may not be aware that U.C. with all its pain and discomfort is a chronic disease. Several investigators[2-6] have shown that the best way to control relapse is to medicate over the long-term with Azulfidine® (sulfasalazine, N.F.)*. Further proof is contained in the new double-blind "Truelove" study.[1]†

Ulcerative colitis patients were symptom-free at the start of this controlled study. All had been maintained on Azulfidine for from one to over five years. During the six-month trial, more than 54% of the placebo group suffered relapse—a rate 4½ times greater than the 12.1% who showed a recurrence of symptoms in the Azulfidine-treated group! The therapeutic action of Azulfidine was credited with the striking difference in these figures. The only side effects among the study group were two cases of nausea and one of headache. (These symptoms ceased without a change in dosage when patients returned to open therapy.)

The authors concluded that maintenance treatment of ulcerative colitis with Azulfidine be continued indefinitely unless contraindicated by side effects.

Observe patients carefully, since in many cases adjustment of dosage will control side effects (see Prescribing Information). Azulfidine is also available in enteric coated EN-tab® tablet form for those patients susceptible to gastric upset.

Over the long haul the best preventative is the proven safety of continuing maintenance treatment.

†Reprint available from Pharmacia.

AZULFIDINE®

(sulfasalazine, N.F.)

AZULFIDINE®
(sulfasalazine, N.F.)
Tablets and EN-tabs®

INDICATIONS: AZULFIDINE (sulfasalazine, N.F.) is indicated in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis. AZULFIDINE EN-tabs are particularly indicated in patients who experience gastrointestinal intolerance after the first few doses of the drug, when such intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites and in those for whom a reduction in dosage does not alleviate the gastrointestinal effects.
CONTRAINDICATIONS: Hypersensitivity to sulfonamides or salicylates. In infants under 2 years. Intestinal and urinary obstruction. Pregnancy at term and during the nursing period. In patients with porphyria.
WARNINGS: The safe use of sulfonamides in pregnancy has not been established. Evaluate benefit to risk carefully when giving sulfonamides during pregnancy, especially at term, since kernicterus may be produced in the newborn. The teratogenic potential of most sulfonamides has not been thoroughly investigated in any species and a significant increase of cleft palate and other bony abnormalities has been observed when certain sulfonamides were given orally to pregnant rats and mice at 7 to 25 times the human therapeutic dose.

Deaths associated with the administration of AZULFIDINE (sulfasalazine, N.F.) have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and CNS changes and fibrosing alveolitis.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders.

Complete blood counts as well as urinalysis with microscopic examination should be done frequently.
PRECAUTIONS: Administer with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia.

Maintain adequate fluid intake to prevent crystalluria and stone formation.
ADVERSE REACTIONS: Adverse reactions have been observed in 5 to 55% of patients included in clinical studies reported in the literature. Experience suggests that with daily dosages of 4 g or more, adverse reactions tend to increase. The most common adverse reactions associated with AZULFIDINE therapy are anorexia, nausea, vomiting, and gastric distress. The following adverse reactions have been reported to occur during therapy with AZULFIDINE.

Blood dyscrasias: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, Heinz Body anemia, purpura, hypoprothrombinemia, "cyanosis," and methemoglobinemia.

Hypersensitivity reactions: Generalized skin eruptions, erythema multiforme (Stevens-Johnson syndrome), parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, pruritus, urticaria, photosensitization, anaphylaxis, serum sickness syndrome, chills, drug fever, periorbital edema, conjunctival and scleral injection, arthralgia, transient pulmonary changes with eosinophilia and decreased pulmonary function, allergic myocarditis, polyarteritis nodosa, and L.E. phenomenon.

Gastrointestinal reactions: Anorexia, nausea, emesis, abdominal pains, diarrhea, impaired folic acid and digoxin absorption, stomatitis, pancreatitis, and hepatitis.

CNS reactions: Headache, vertigo, tinnitus, hearing loss, peripheral neuropathy, transient lesions of posterior spinal column, transverse myelitis, ataxia, convulsions, insomnia, mental depression, hallucinations and drowsiness.

Renal reactions: Crystalluria, hematuria, proteinuria, and nephrotic syndrome. Toxic nephrosis with oliguria and anuria.

Incidents of alopecia and reduction in sperm count and viability have also been reported.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross sensitivity may exist with these agents.

AZULFIDINE (sulfasalazine, N.F.) produces an orange-yellow color when the urine is alkaline. Similar discoloration of the skin has also been reported.
SUPPLIED: Tablets and EN-tabs (enteric-coated) 0.5 gm. in bottles of 100 and 500. Also available as Azulfidine Unit Dose in boxes of 100's and 1000's.
IMPORTANT: See full prescribing information before administering AZULFIDINE.

References:
1. Dissanayake, A.S. and Truelove, S.C.: Gut 14:923-926, Dec. 1973.
2. Bargen, J.A.: Amer. Surg. 28:630-637, Sept. 1962.
3. Hightower, N.C., Jr., et al.: Amer. J. Digest. Dis. 3:722-733, 861-876, 931-941, Oct., Nov., Dec. 1958.
4. Roth, J.L.A.: Chapter 69, in Bockus, H. (ed.): Gastroenterology, Vol. II, W.B. Saunders Company.
5. Riis, P., et al.: Scand. J. Gastroenterol. 8:71-74, 1973.
6. Goldstein, F. and Thornton, J.J.: Consultant 14:96-103, July 1974.

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MEETINGS OF INTEREST

43rd Annual Convention, American College of Gastroenterology, The Marriott, Denver, Colo., 24-27 September 1978.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, The Marriott, Denver, Colo., 28-30 September 1978.

One Day of Gastroenterology, Postgraduate Course co-sponsored by the American College of Gastroenterology, the Southern Medical Association. Georgia World Congress Center, Atlanta, Ga., 11 November 1978.

in irritable colon*

When stress makes waves for the spasm reactor...

A normal reaction to emotional stress is a marked increase in both the strength and frequency of wave-like contractions of colonic motility.[1] However, in the patient with irritable bowel syndrome, this psychovisceral reaction is of greater intensity and duration than normal.[2]

The result can be G.I. spasm.

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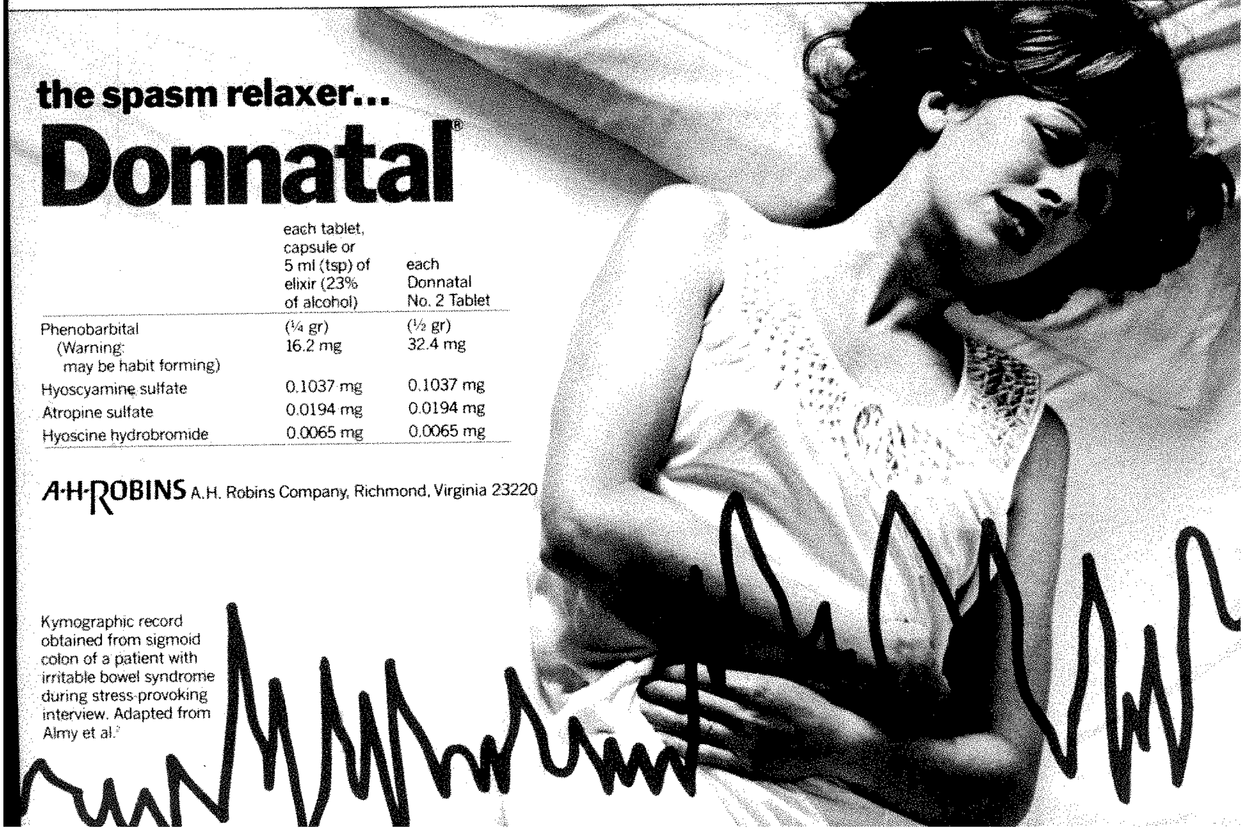
References: 1. Almy, T.P., Kern, F., and Tulin, M.: Alterations in colonic function in man under stress. II: Experimental production of sigmoid spasm in healthy persons. *Gastroenterology* 12(3):425-436, 1949. **2.** Almy, T.P., Hinkle, L.E., Berle, B., et al.: Alterations in colonic function in man under stress. III: Experimental production of sigmoid spasm in patients with spastic constipation. *Gastroenterology* 12(3):437-449, 1949.

*Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindicated in patients with glaucoma, renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy), or a hypersensitivity to any of the ingredients. Blurred vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur at higher dosage levels, rarely at the usual dosage.



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Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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VOLUME 69 APRIL, 1978 NUMBER 4

New Dimensions in the Laboratory Diagnosis of Pancreatic Disease*

J. EDWARD BERK, M.D., D. Sc., F.A.C.G.†
Irvine, CA

INTRODUCTORY COMMENTS

The privilege of presenting the First David C. H. Sun Lecture of the American College of Gastroenterology is both an honor and a personal pleasure. It not only allows me to join the College in recognizing one of its distinguished Fellows but it also provides me an opportunity to express my admiration for a friend and colleague of many years.

Modifications in older laboratory methods and newly conceived laboratory technics, aimed at detecting the existence of pancreatic disease, have appeared in almost crescendo-like fashion within recent years. These developments have broadened the dimensions and sharpened the accuracy of the laboratory approach to the diagnosis of pancreatic disease. It is with the fundamental concepts and the clinical application of some of the more recent advances that this presentation will be concerned. The data to be described are drawn, in large part, from observations made in the Gastrointestinal Research Laboratory of the University of California, Irvine. Vital roles in these studies have been played by several associates, particularly Dr. Louis Fridhandler, as well as a number of Research Fellows. I wish, therefore, to speak at this time primarily as the representative of this group.

ISOAMYLASE ANALYSIS

The most widely and frequently employed laboratory measure for pancreatic disease is assay of amylase activity in serum and urine. Despite its clearly established usefulness, determination of the activity of this enzyme suffers several limitations. Among these are: 1. the relatively brief duration of the rise in amylase activity in pancreatitis; 2. the occurrence of elevated amylase levels in situations in which the pancreas does not seem to be involved,[1] 3. the rise in activity that may be seen after administration of analgesics[2] and 4. the influence of stress on amylase activity as evidenced by a rise in this activity after steroid hormone administration.[3, 4] Perhaps the greatest shortcoming, however, is its lack of specificity with respect to origin. This handicap has spurred efforts in recent years

---

* First David C. H. Sun Lecture presented at the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, New Orleans, LA, 27 October 1977.

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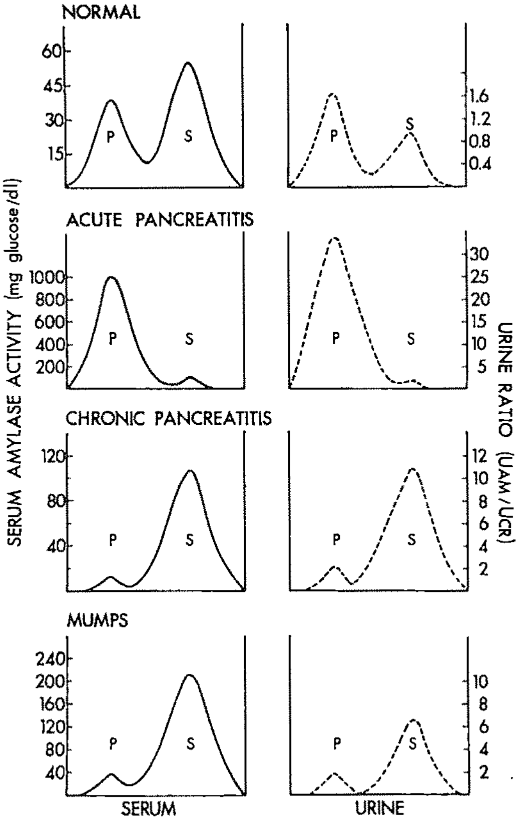

Fig. 1—Isoamylase patterns classically found in the serum and urine of normal subjects and in patients with the clinical disorders noted. The configurations for urine represents the ratios of the isoamylases for the isoamylases to creatinine in the urine. (*Reproduced with permission of the publisher, Lea & Febiger, Inc., from Developments in Digestive Diseases* (1), Fig. 1, Chapter 8).

to devise a reliable, simply performed test that would specifically measure the amylase form arising from the pancreas. While not yet fully achieved, new approaches have been formulated that improve the specificity and enhance the diagnostic efficacy of amylase assay.[5, 6]

METHODS

Chromatography:—Using ion exchange chromatography (DEAE-Sephadex A-50,[7] or QAE-Sephadex A-50,[8] after preliminary purification of the serum or urine amylase by passage through Sephadex G-100) two major amylase peaks are found in both serum and urine (Fig. 1). The first of these peaks occupies the same chromatographic position as the single peak recovered from pancreatic extract and hence has been designated "P-type". The second principal peak is in the same chromatographic position as the solitary peak of amylase found in saliva or parotid gland extract and hence has been designated "S-type". Total pancreatectomy in man[7, 9] and the rat[10] results in disappearance of the P-type component. This has been taken as fairly convincing evidence that the P- type isoamylase arises only in the pancreas. By contrast, S-type isoamylase has been demonstrated in many different tissues[5, 6, 9, 11-14] and is not confined to the parotid gland and saliva. In this regard, it should be noted that a small amount of the total amylase activity recoverable from the pancreas (0.8-1.7% of total amylase activity) resembles S-type isoamylase in its chromatographic mobility.[13]

S-type isoamylase usually is present in slightly greater amounts than P-type in normal serum (Fig. 1). In normal urine, by contrast, P-type isoamylase is ordinarily the dominant form (Fig. 1).[7] Normal ranges of values have been established for the activities of total serum amylase and the chromatographically resolved principal isoamylases in human serum and urine.[8] These values serve as standards against which the findings in abnormal states may be compared.

The disadvantages of the chromatographic method for isoamylase analysis are the relatively large samples of serum required (10 ml., unless marked hyperamylasemia exists) and the complexity of the determination. Indeed, the method in its present technical form does not lend itself to general clinical use, despite its proven value as a research tool.

Electrophoresis:—Electrophoretic methods for measuring isoamylases vary in such factors as: 1. the type of supporting medium (polyacrylamide gel, cellulose acetate membranes, agar gel, agarose gel); 2. the buffer employed (Tris, phosphate, veronal); 3. the hydrogen ion concentration (pH) used and 4. the ionic strength. Depending on the methodology used, two major peaks and as many as two to four minor peaks of amylase activity may be demonstrated in normal human serum.[5, 6] Amylases with mobility corresponding with the peaks found in purified pancreatic extracts or secretion are referred to as "P" isoamylases and numbered consecutively; those with mobilities corresponding to the peaks found in purified salivary tissue or saliva are designated "S" isoamylases and are also consecutively numbered.

Multiple electrophoretic peaks of amylase activity are also demonstrable in normal human urine. These peaks are likewise designated "P" and "S", respectively, on the basis of their mobility resemblance to the peaks found in purified pancreatic and salivary material. As with the corresponding peaks in the serum, the urinary "P" and "S" peaks are numbered sequentially in order of their electrophoretic position.

A problem in the use of electrophoresis to distinguish the isoamylases arises when there is an admixture of isoenzyme forms,[6, 16] as in serum. As pointed out by Townes,[16] slight differences in electrophoretic mobility may be obscured and some of the isoamylase forms become indistinguishable.

Isoelectric focusing:—This method discriminates among the isoamylases on the basis that each isoamylase will migrate in a pH gradient to a position determined by its "isoelectric point" (pI) and there it will remain. Resolution may be very high with this method and various isoamylases may be distinguished on the basis of discernible, albeit slight, differences in pI. Thus, as many as six salivary isoamylases and eight pancreatic isoamylases have been described in human serum by means of isoelectric focusing.[17] Based on the observations thus far reported using this technic, it would seem that complete or very substantial separation of P and S-type isoamylase is possible but has not been consistently obtained.[6]

Other methods:—Other technics have also been used to study isoamylases in body fluids but these do not appear to have clinical application. Among the properties that have been studied are *action patterns, heat lability* and *immunological behavior.*[6] With respect to the immunologic approach and the current popularity of radioimmunoassay methods, it should be noted that all studies to date dealing with antigen-antibody reactions have indicated considerable overlap in the responses of the principal isoamylases. At present, therefore, this overlap and the discriminatory uncertainty stemming from it, are unsolved issues curbing the practical clinical application of an immunological procedure.

More recently, a protein recoverable from wheat has been shown to inhibit the activities of the isoamylases, particularly that of the S-type.[18] Utilization of this inhibitory protein to distinguish the chief isoamylase forms on the basis of this difference in inhibitory action requires further evaluation. Should it prove reliable, clinical application of the inhibitory test may simplify isoamylase analysis considerably.

CLINICAL APPLICATION

The distribution pattern of the isoenzymes of amylase in a variety of normal secretions and tissues of the body have been delineated by means of one or the other of the basic assay methods earlier described. Similar notations have been made in various disease states.[5, 6] The information so obtained has proved helpful in unraveling certain clinical problems and conditions and has opened the way to new diagnostic approaches.

Acute pancreatitis:—The amylase pattern in the serum and urine of patients with acute pancreatitis is featured by a dominant rise in P-type isoamylase activity (Fig. 1). In some cases studied by the chromatographic method, a rise in serum S-type isoamylase has also been observed.[7] The origin of the S-type fraction noted in these cases, however, has not yet been fully established.

The wide range in *percentage* of P-type isoamylase in the urine of normal persons makes it difficult to assess the significance of an increase in relative percentage of P-type isoamylase. For this reason, other methods have been employed to evaluate the situation in the urine. These will be considered in detail later.

Pancreatic exocrine insufficiency:—The classical isoamylase pattern in this condition is the reverse of that in acute pancreatitis; P-type isoamylase in this situation tends to be reduced rather than increased (Fig. 1). A somewhat different approach reflecting the same change is that suggested by Aw, et al.[19] These investigators found that determination in the urine of the ratio of P-type to S-type isoamylase (P/S), using agar gel electrophoresis, was of value. In 34 subjects without chronic pancreatitis, the P/S ratios ranged from 0.9-3.4, whereas the ratios in seven of eight patients with chronic pancreatitis did not exceed 0.6. In our laboratory, however, P/S ratios determined by means of ion exchange chromatography in 123 normal urines displayed a much greater range (0.4-15.7) than that found by Aw and his group with their technic.[8]

Parotitis:—The isoamylase pattern in acute epidemic parotitis (mumps) is featured by a sharp rise in S-type isoamylase (Fig. 1). In contrast, destruction or removal of salivary gland tissue results in diminution but not total disappearance, of S-type isoamylase.[6, 9, 11, 20] Persistence in the serum of some S-type activity in such circumstances indicates that the so-called S-type isoamylases do not originate solely in the salivary glands; in all likelihood, they arise from other tissues as well.

Postoperative hyperamylasemia:—Observations have been reported by both electrophoretic and chromatographic methods that the amylase rise not infrequently noted in the immediate postsurgical period is due in some cases to heightened activity of S-type isoamylase.[21] This means, then, that a postoperative rise in serum amylase activity, even after an abdominal procedure, is not necessarily an indication of complicating pancreatitis. The demonstration by isoamylase analysis that the increased amylase activity in the serum is due primarily to a rise in S-type isoamylase would not only be reassuring on this point, but would also be influential in determining the therapeutic attitude to adopt.

Amylase changes after ERCP:—Rise of amylase activity in the serum and urine after endoscopic retrograde cholangiopancreatography (ERCP) has been noted repeatedly.[22-24] The number of instances of clinically apparent acute pancreatitis developing after this diagnostic procedure, however, constitutes but a very small fraction of those who display hyperamylasemia or hyperamylasuria after the study. The data currently available regarding the isoamylase distribution in those patients showing amylase increases after ERCP is still quite limited. Such data as are available indicate that when the pancreatic duct is radiologically visualized, the rise in amylase after ERCP is most often the result of a rise in P-type isoamylase. For example, in our own studies of patients undergoing

ERCP (only partially reported at this time[25]) the isoamylase affected was P-type in all 18 patients in whom the pancreatic duct was visualized, and in whom postprocedural hyperamylasemia ensued.

The conclusion that these observations seem to mandate is that post-ERCP hyperamylasemia must be viewed as reflecting pancreatic alteration of some type if the procedure succeeded in opacifying the pancreatic duct.

Acute alcoholism:—The occurrence of hyperamylasemia or hyperamylasuria during an episode of acute alcoholic intoxication would very likely be interpreted by the clinician as evidence of alcohol-induced pancreatitis. Preliminary observations conducted in our laboratory in 129 patients (142 serum samples) indicated that the frequency of occurrence of hyperamylasemia in such circumstances is surprisingly high (11 of the 129 patients or 8.5%). Even more arresting were the findings on isoamylase analysis. This analysis was carried out in 78 serum specimens from 70 subjects. A rise in one or the other of the two principal isoamylases was found in 11 (14.1%) of the 78 specimens. The rise was confined to the S-type in six of the 11, and in one case was in both S- and P-types. Similarly, isoamylase analysis in 11 inebriated patients found to have hyperamylasemia showed that of 10 evidencing a rise above the upper limit of normal in one or the other or both of the chief isoamylases, the rise in six (60%) was of S-type only.

These preliminary observations bear importantly on the interpretation of hyperamylasemia in inebriated patients.[6] Judged from them, it would appear that increased serum amylase activity during acute alcoholic intoxication need not necessarily reflect pancreatic damage. Rise in amylase levels may be the result instead of alcohol-induced changes in the salivary glands, or in other structures that have the capacity to form amylase with a chromatographic mobility pattern resembling S-type isoamylase.

Amylase changes after opiates:—As noted earlier, total amylase activity may rise in the serum following administration of an opiate,[2] an effect that may cause confusion in the interpretation of hyperamylasemia in a patient with abdominal pain. The mechanism conceptualized for such rises is analgesic-induced constriction of the choledochal sphincter and the pancreatic ducts, causing a rise in pressure within the smaller ducts with resultant regurgitation of amylase into the serum.

To test the validity of this postulated mechanism, we studied the amylase changes in a group of 91 heroin addicts admitted to the hospital with symptoms of acute overdose of heroin.[13] Hyperamylasemia was recorded in 17 (19%). Contrary to our expectation, however, when isoamylase analysis was done by the chromatographic method on the serum of these 17 heroin addicts with hyperamylasemia, S-type isoamylase elevation was the dominant change, occurring in 15 of the 17 patients; P-type elevation alone was found in one patient and essentially equivalent P- and S-type isoamylase elevations in the remaining patient.

On further analysis, it was found that 13 of the 17 addicts with hyperamylasemia also had acute respiratory distress and associated pulmonary changes. This, together with observations we had made earlier regarding cancer of the lung (see following discussion on tumor-associated hyperamylasemia), led to special studies, as yet unpublished, on normal human lungs. These extended and confirmed observations reported by others to the effect that the lungs contain amylase resembling S-type in electrophoretic and chromatographic behavior.[26]

The nature and origin of the amylase increase in the serum after opiates and other analgesic drugs thus remains unresolved. Before these matters can be fully clarified, isoamylase analysis will have to be done in selected subjects receiving analgesics who are free of any pulmonary disease or other pulmonary derangement.

Tumor-associated hyperamylasemia:—Many reports have appeared over the years indicating that hyperamylasemia may occur in association with cancer arising in various tissues, especially cancer of the lung.[14] Our own observations now extend to nine patients with cancer-associated hyperamylasemia (three in the lung, four in the pancreas and two in the colon). Isoamylase analysis conducted in eight of these patients disclosed that the dominant isoamylase was S-type in three and P-type in four; in one patient both isoamylases were elevated about equally. A surprising and rather impressive finding was that the amylase elevation in two of the patients with primary pancreatic cancer consisted essentially of S-type isoamylase. It should be noted, however, that total amylase activity in one of these patients was only in the equivocally elevated range for the method employed.

Explanation for the frequency with which the S-type isoamylase predominates in patients with cancer and associated hyperamylasemia is not yet at hand. The fact alluded to earlier that normal lung apparently contains an S-type isoamylase may provide a basis for the S-type dominance seen in particular with primary cancer of the lung that is associated with hyperamylasemia. It is necessary to bear in mind, however, that isoamylases with identical chromatographic and electrophoretic mobility characteristics, or similar isoelectric focusing properties, need not be identical with regard to all their properties. It has been shown, for instance, that the isoamylase extracted from lung cancer tissue displays certain kinetic and other biochemical properties that differ from the isoamylase recovered from saliva.[27] Much yet remains to be learned, therefore, before the amylase changes found in some patients with cancer can be fully interpreted and their significance assessed.

Another notable and perhaps important finding made in our laboratory has to do with subcomponent isoamylases in patients with tumor-associated hyperamylasemia. Using a special series of chromatographic studies,[28] we have demonstrated the occurrence of an unusual isoamylase, designated "Y"-type,[29] in three patients. One of these patients had primary cancer of the lung and two had primary cancer of the pancreas. In addition to these three cancer patients, we have thus far found the peculiar Y subcomponent isoamylase only in some samples of human milk. Special studies failed to disclose it in normal subjects, or in patients with a variety of clinical disorders.[29] The significance of this Y-type isoamylase subcomponent and its relationship to cellular growth and replication, pose challenging questions, therefore, that remain to be answered.

S-type hyperamylasemia:—"Macroamylasemia" in its classical form[30] is of clinical interest primarily because it requires consideration in the differential diagnosis of persistent hyperamylasemia. Isoamylase analysis has now made it clear that the problem is more complex. S-type isoamylase may accumulate in the serum and produce all the indirect signs of macroamylasemia, yet fail to show a circulating macroamylase when the latter is tested for directly.[31] "S-type hyperamylasemia" therefore, has now emerged as still another biochemical aberration that must enter into consideration in the interpretation of hyperamylasemia and in the differential diagnosis of pancreatic disease.

Renal insufficiency:—Evidence at hand indicates that only a portion of the amylase in the blood is excreted through the kidneys and into the urine.[32, 33] Even so, it has long been recognized that disruption or impairment of the renal excretory apparatus may cause the level of circulating amylase to rise.[34-36] With the advent and application of isoamylase analysis, it has been made clear that both the chief isoamylases may become elevated when there is impairment in renal excretion.[34] Hence, in distinguishing hyperamylasemia due to renal insufficiency alone from that due to pancreatitis complicating renal insufficiency, the finding by isoamylase analysis of a preponderant rise of P-type isoamylase may be supporting evidence for complicating pancreatitis.[34]

Miscellaneous clinical problems:—The ability now available to separate the principal isoamylase forms and to determine whether one or the other, or both, exceeds the established upper limit of normal, has emerged as a highly useful laboratory procedure in puzzling situations encountered clinically. It is of particular value in patients with abdominal pain or other symptoms suggesting the possibility of pancreatic disease. The application of isoamylase analysis to the elucidation of these clinical problems has proved in our hands[5, 6] and in those of others,[5, 6, 9, 37, 38] to be clinically valuable and informative.

SUMMARY

Isoamylase analysis of serum, urine, or other body fluids provides a new dimension in the diagnosis and differential diagnosis of pancreatic disease. Determination of amylase activity has been endowed with greater specificity by the ability to identify amylase arising in the pancreas (P-type). Through the use of this type of analysis, much clinically useful and enlightening information has been obtained. The method has also been shown to be of value in unraveling individual clinical problems in which hyperamylasemia is a feature. Unfortunately, the technical methods currently employed do not lend themselves to ready clinical application. Concentrated interest, demonstrated in this area and the studies now in progress, however, give every reason to hope that a simple, easily and rapidly performed procedure that reliably and specifically identifies and measures P-type isoamylase will soon be forthcoming.

AMYLASE CLEARANCE/CREATININE CLEARANCE RATIO

The occurrence of hyperamylasuria in acute pancreatitis has long been appreciated. More refined observations made in recent years have established that the kidneys, in the presence of acute pancreatitis, have a propensity to excrete amylase to a degree even greater than creatinine. This phenomenon has been utilized as the basis for a test for acute pancreatitis that consists simply of measuring amylase and creatinine concentrations in simultaneously obtained serum and urine samples and then computing from these values the ratio of amylase clearance to creatinine clearance (Cam/ Ccr).[39] An elevated Cam/Ccr in a patient with signs and symptoms suggestive of acute pancreatitis, especially when attended by hyperamylasemia, provides confirmatory evidence of acute pancreatitis.[39] Although the adjunctive value of the Cam/Ccr in the detection of acute pancreatitis is well substantiated,[39-44] it should be borne in mind that the test is neither infallible nor altogether specific.[45, 46]

In our laboratory, positive clearance ratios were found in only 40 (62.5%) of 64 patients with hyperamylasemia who were given a final diagnosis of acute pancreatitis. Time of performance of the test, however, appears to be of importance and in many of our patients the clearance ratio was not determined until well after the onset of the disease. A much higher percentage of positive tests would probably have been obtained were all tests done within 48 hours of the onset of symptoms.

On the opposite side, false positive clearance ratios were recorded in 28 (30.4%) of 92 patients with hyperamylasemia in whom the final diagnosis proved to be a disorder other than acute pancreatitis. This high frequency of false positive tests is also probably not reflective of the actual situation obtaining in clinical practice because of the purposeful inclusion in our series of a number of instances of disorders now recognized as being associated with elevated Cam/Ccr ratios in the absence of pancreatitis, such as uncontrolled diabetic ketoacidosis and burns.[45] Nevertheless, it is difficult to avoid concluding that false positive results must occur.

Still another factor affecting the calculated clearance ratio is the technic employed for amylase assay. Thus, Levitt and his associates[47] have shown that the degree of amylase activity in the urine is more efficiently measured by a saccharogenic assay method than by iodometric or chromatogenic technics. Hence, the Cam/Ccr may well be influenced by the assay method employed and interpretation of the ratio must be by comparison only with the range of normal values established for the specific technic used.

URINARY AMYLASE/CREATININE RATIO

The ratio of urinary amylase to urinary creatinine (Uam/Ucam) also tends to be increased during acute pancreatitis.[6] This rise probably reflects little more than the existence of hyperamylasemia with increased urinary excretion of the enzyme. Nevertheless, we have found that this simply determined ratio is a highly useful and dependable means of recognizing the existence of relative hyperamylasuria.

To date we have made this determination in 136 normal individuals, expressing the amylase value in terms of mg. of glucose/dl.[48] and creatinine as mg. of creatinine/dl. In these normal persons, the Uam/Ucr ratios ranged from 0.42-7.41 with a mean of 2.6. By contrast, the ratio in 51 patients with acute pancreatitis ranged from 3.2-633 with a mean of 51.0. High Uam/Ucr ratios have also been noted by us in a variety of other clinical conditions associated with hyperamylasemia, such as burns, cancer, heroin addiction, and after ERCP.

Of particular interest has been our finding of an elevated Uam/Ucr ratio in some patients with acute pancreatitis in whom the Cam/Ccr ratio was within the normal range. This was especially evident in patients followed serially. Thus, in 14 patients with acute pancreatitis in whom more than one serum sample was examined during the acute episode, the Cam/Ccr in nine fell to values within the normal range as the acute pancreatitis subsided, while the Uam/Ucr ratio continued to remain elevated. It would seem, therefore, that the Uam/Ucr ratio may be especially helpful in the subsiding phase of acute pancreatitis when the amylase levels in the serum may have reverted to normal and the Cam/Ccr ratio is no longer increased.

Another interesting and clinically useful observation is the occurrence of normal Uam/Ucr ratios in cases of macroamylasemia and S-type hyperamylasemia, despite the existence of considerable hyperamylasemia.

SCREENING TEST FOR PANCREATIC-TYPE HYPERAMYLASURIA

Based on the concept that increased amylase in the urine caused by pancreatic disease will be marked by a larger proportion and a greater amount of P-type isoamylase, we have devised a screening test for P-type hyperamylasuria.[49] The test is fundamentally a chromatographic procedure that takes approximately 1½-2 hours to complete. The hope is that it will serve as a screening test for pancreatic disease reflected in the appearance of increased amount of P-type isoamylase in a random sample of urine. Such a screening method would have particular value in patients presenting with abdominal pain whose cause when initially seen needs to be established.

Thus far we have carried out the test within 48 hours of the onset of symptoms in 84 patients who, when initially seen, were either given an admitting diagnosis of acute pancreatitis, or who had abdominal pain for which acute pancreatitis was considered to be one possible explanation. The test procedure employed in the first 43 patients was the one originally constructed. A positive test was obtained in 17 (81%) of the 21 patients in this group who were given a final diagnosis of acute pancreatitis. All of the 22 patients who were found subsequently to have a disorder other than acute pancreatitis gave negative tests.

More recently, we modified the test and simplified its performance. The modified test has to date been conducted in 41 patients in the same cricumstances. Positive results were obtained in 17 (77%) of the 22 patients classified ultimately as having acute pancreatitis. Again, no positive test was obtained in any of 19 patients with nonpancreatic disorders as established by subsequent studies.

We are encouraged to feel from these still unpublished data that the test for P-type hyperamylasuria in the urine holds promise as a screening procedure for acute pancreatitis. A positive test would be supportive of this disorder and more specific for pancreatic derangement than simple measurements of the output of total amylase in the urine. A negative test, on the other hand, especially if the test is not performed until more than 48 hours after the onset of symptoms, would not exclude pancreatic involvement.

CONCLUSIONS

The laboratory diagnosis of pancreatic disease has been made more precise by certain modifications in older methods and by the introduction of a variety of new technical procedures. The principal human isoamylases may now be distinguished and their activities in serum and urine measured. A test has been devised which helps indicate the presence of acute pancreatitis by showing relatively increased excretion of amylase in the urine as compared with creatinine. The ratio of amylase to creatinine in the urine appears to be a good index of relative hyperamylasuria. A screening test for pancreatic-type hyperamylasuria has been formulated that allows increased urinary excretion of this isoamylase to be identified. These additions and developments have sharpened the interpretation of hyperamylasemia and hyperamylasuria and have added new dimensions to the laboratory diagnosis of pancreatic disease.

ADDENUM

A report has recently appeared describing a radioimmunoassay for S-type isoamylase that is claimed to show little cross-reactivity.[50]

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On the Appearance, Levels and Regulation of Pancreatic Enzyme Serum Concentrations

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INTRODUCTION

It is generally accepted though not proved, that pancreatic ferments appear in the blood as waste products en route to excretion by the kidney and that their respective concentrations represent an equilibrium between the rate of delivery of each enyzme from the pancreas and the rate of filtration of the enzyme by the kidney.

This report attempts to elucidate some factors regulating serum pancreatic enzyme concentrations and comments upon their possible metabolic significance.

MATERIAL AND METHODS

The following serum determinations were made in the patients and experimental animals of this study: 1. amylase concentration in whole (AWHS) and diluted serum (ADS)[1]; 2. tryptic (T) and antitryptic inhibitor activity (AT)[2]; 3. 17-hydroxycorticosteroid (17-HOCS) concentration in plasma.[3] These determinations were performed upon a clinical series of 29 control subjects and 101 patients with proved chronic relapsing pancreatitis, 29 of whom were treated for their pain with anabolic steroids, i.e. cortisone and metandrostendiol for four to six weeks. Similar serum studies were also performed upon six dogs weighing 5-10 kg. following injection of 40 mg. of crystalline elastase (dissolved in 2 ml. saline) into the ligated duct of Wirsung.

Some authors have determined serum enzyme inhibitors by direct methods, i.e. titration of serum against the crystalline enzyme,[4, 6] by immunoassay[6] and by indirect method, i.e. dilution methods including electrophoresis.[7] The latter technic follows the report of Dreiling, et al in 1963,[7] in which the combined amylase activities of the serum protein fractions, obtained by electrophoresis, was observed to be three to four times greater than the activity measured in whole serum not subjected to fractionation. This difference was noted for the sera of control patients, patients with pancreatic cancer and patients with chronic but not acute pancreatitis. In the latter, the total fractional amylase activity is of the same order of magnitude as the activity of whole nonelectrophoresed serum. The difference between this sum total diluted (fractional) activity and undiluted (whole) activity was a measure of the serum content of amylase enzyme inhibitor. Tuzhilin and Petrova confirmed these observations and reported, in addition, that the dilution augmentation of both serum amylase and trypsin activity could be abolished by the addition of trasylol to the diluent (Table I).[8] We have chosen to measure enzyme inhibitor activity by determining, thus, the augmentation of activity of the serum upon dilution. Laboratory support of the validity of this method is provided in Figure 1, in which the expected exponential decline in

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TABLE I

INFLUENCE OF DILUTION OF SERUM BLOOD BY SALINE OR TRASYLOL ON AMYLASE ACTIVITY

Amylase activity of serum (in units)				
Whole serum		Diluted (1:2) serum		P
Number of patients	M ± SD	Number of patients	M ± SD	
Dilution by saline				
9	56 ± 18	9	128 ± 42	< 0.001
Dilution by trasylol				
8	89 ± 24	8	105 ± 37	> 0.10

crystalline trypsin activity (Spofa, Czech.) is compared with the activity curve with dilution of a crystalline trypsin-trasylol (Bayer) mixture. The initial activity of the crystalline trypsin is markedly decreased due to inhibition by trasylol. Initial dilution removes the degree of inhibition by diluting inhibitor effect; further dilution, dilutes both enzyme activity and inhibitor with little change in observed enzyme activity.

RESULTS

In Table II the amylase activity of whole serum (AWS) is compared to that of serum diluted 1:2 by phosphate buffer (ADS) for nine patients without illness and 51 patients with exacerbation of chronic relapsing pancreatitis. The ratio of ADA/AWS has been calculated for both groups. The data indicate that the average amylase activity as measured for whole serum in the patients with exacerbated chronic pancreatitis was higher than in normals. Moreover, serum dilution in these patients only slightly increased amylase activity, while, in the control patients, dilution more than doubled amylase activity, viz ADS/AWS values of 1.26 and 2.30 respectively, suggesting decreased serum amylase inhibitor activity in these patients with chronic pancreatitis. Similar data for serum trypsin-like activity and trypsin-inhibitor activity have been reported by us for these patient groups.[9]

Table III compares serum tryptic and amylase activity before and after controlled diet therapy (high protein—40 patients, normal protein—20 patients) in 60 patients with chronic relapsing pancreatitis. High protein diet has been previously shown by us to beneficially affect the clinical complaints of these patients.[9] The data clearly indicate a statistically significant decrease in serum tryptic activity as well as a significant increase in trypsin inhibitor after high protein diet. Although a distinct trend towards decreased amylase activity following high protein diet is shown by the data, the decrease is not statistically significant. On the other hand, no significant changes in serum tryptic, trypsin inhibitor, or serum amylase activity were noted in the patients with chronic relapsing pancreatitis kept in a normal protein diet.

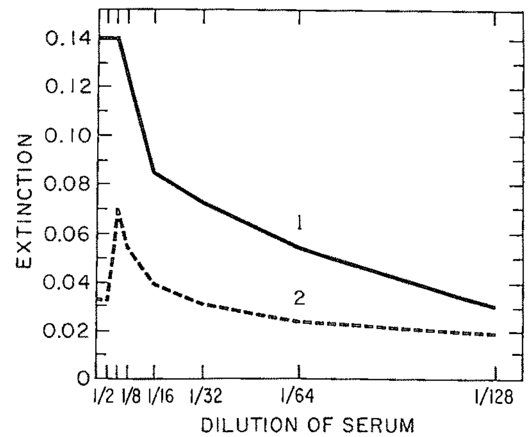

Fig. 1—The curves of dilution of (1) trypsin, "Spofa" (Czech.) and (2) trypsin mixed with trasylol (Bayer). Substrate is DL-benzoil-arginine-p-nitroanilide. Initial dilution of trypsin is 50 gamma in 1 ml.; initial solution of trasylol is 250 KI in 1 ml.

In Table IV, plasma 17-hydroxycorticosteroids (17-HOCS), serum trypsin-like (TLA) and antitrypsin activity (ITLA) are compared for healthy subjects (12) and patients (21) with chronic relapsing pancreatitis. The data show, in accordance with previous reports[10, 11] statistically significant differences in the data of each group and also parallel changes in level of 17-HOCS and ITLA activity. Table V presents the effects on these parameters of feeding a high protein diet to these 21 patients with chronic pancreatitis. The data indicate the response to the diet to be statistically significant, parallel with increases of plasma 17-HOCS and serum antitryptic activity associated with a fall in serum trypsin-like activity. Finally, treatment of these patients with steroids (cortisone)[12] and anabolics (metandrostendiol)[13] resulted in a 20-29% decrease in serum tryptic and amylase activity as well as a 20% increase in trypsin and amylase inhibitor activity.

In Table VI, average serial activity of serum amylase (AWS) and diluted serum amylase (ADS) as well as the calculated ADS/AWS ratio is presented for six dogs in whom acute pancreatitis was induced by injection of purified elastase into the ligated main duct. Progressive decreases in ADS and ADS/AWS ratios are observed and become statistically significant at the end of a month, at which time autopsy revealed an indurated pancreas with plaques of fat necrosis scattered throughout the pancreas and neighboring viscera.

COMMENT

The concepts that pancreatic ferments appearing in the blood are inactive enzymes cast into the bloodstream as a consequence of exocrine secretion according to an exocrine-endocrine secretion ratio and that these inactive enzymes are then carried to the kidney for secretion are no longer tenable. On the contrary there is increasing physiologic evidence that: 1. Endocrine secretion of these exocrine enzymes is an active process occurring through a cytoloplasmic pathway at the base of the acinar cell completely independent of the zymozen granular system of Hokin-Palade.[14] 2. The acinar cell membrane and the gut epithelia are freely permeable to these enzymes in both directions.[14] 3. There exists an entero-pancreatic circulation of pancreatic ferments which provides a physiologic feedback mechanism in the regulation of secretion.[14] 4. There exists enteric secretion of enzymes following pancreatic duct ligation with significant contribution to maintenance of digestion, a so-called passive enzymatic excretory process.[15] 5. That pancreatic ferments actively participate in such metabolic processes as glycogen synthesis[16-19] (amylase), lipolysis[20] (lipase) and blood coagulability[21] (trypsin). 6. That for amylase, at least, there is evidence of active metabolism in both liver and kidney.

Accepting a physiologic role for serum pancreatic ferments, the simplistic hypothesis that their concentrations and activity would be regulated by the summation of

TABLE II

RATIO OF AMYLASE ACTIVITY IN DILUTED (ADS) AND WHOLE (AWS) SERUM IN HEALTHY PERSONS AND IN PATIENTS WITH CHRONIC EXACERBATED PANCREATITIS

	Amylase activity in serum blood of		
	Diluted serum (1:2) (ADS)	Whole serum (AWS)	ADS/AWS
Healthy persons (9 persons)	128	56	2.3
Patients with chronic exacerbated pancreatitis (51 patients)	186	146	1.26

TABLE III

CHANGES OF ENZYMES' ACTIVITY IN SERUM BLOOD OF PATIENTS WITH CHRONIC RELAPSING PANCREATITIS BEFORE AND AFTER TREATMENT BY HIGH PROTEIN DIET

	Before treatment	After treatment	
	M ± SD	M ± SD	P
	Diet with high protein content (40 patients)		
Trypsin-like activity (in med.)*	11.7 ± 7.0	6.6 ± 4.5	< 0.05
Inhibitor trypsin (in med.)	472 ± 168	538 ± 130	< 0.05
Amylase (in units)	122 ± 69	109 ± 56	> 0.10
	Diet with normal content of protein (20 patients)		
Trypsin-like activity (in med.)	12.4 ± 8.3	11.2 ± 7.6	> 0.10
Trypsin inhibitor (in med.)	464 ± 175	431 ± 72	> 0.10
Amylase (in units)	104 ± 38	152 ± 218	> 0.10

* med = milliunits.

such factors as: 1. the presence or absence of pancreatic inflammation,[16] 2. the presence or absence of pancreatic duct obstruction,[16] 3. the rate of ferment delivery of stimulated pancreatic parenchyma into the interstitial tissues[16] and 4. the rate of filtration of pancreatic ferment into the urine,[16] surely must be an oversimplification of the facts, completely overlooking the physiologic data indicating: a. enzyme activators[22] in the blood, e.g. albumin; b. active pancreatic enzyme inhibitors in the blood of nonpancreatic origin,[23] e.g. trypsin inhibitor[24] and serum amino acids;[25] c. pancreatic enzyme inhibitors of pancreatic origin,[23] e.g. amylase inhibitors,[7, 8] elastase

TABLE IV

17-Hydroxycorticosteriods (17-HOCS), Trypsin-like Activity (TLA) and Inhibitor Trypsin-like Activity (ITLA) in Serum Blood and in Plasma of Healthy Persons and Patients with Chronic Relapsing Pancreatitis

	Healthy persons		Patients with pancreatitis		P
	Number of patients	M ± SD	Number of patients	M ± SD	
17-HOCS (gamma %)	10	16.1 ± 2.4	21	8.7 ± 2.05	< 0.001
TLA (milliunits)	12	2.52 ± 1.28	20	9.5 ± 5.1	< 0.001
ITLA (milliunits)	12	499 ± 78	20	234 ± 102	< 0.001

TABLE V

17-Hydroxycorticosteriods (17-HOCS), Trypsin-like Activity (TLA) and Inhibitor Trypsin-like Activity (ITLA) in Plasma and Serum Blood in Patients with Chronic Relapsing Pancreatitis Before and After Treatment by High Protein Diet (HPD)

	Before treatment by HPD		After treatment by HPD		P
	Number of patients	M ± SD	Number of patients	M ± SD	
17 HOCS (gamma %)	21	8.7 ± 2.05	21	16.4 ± 5.8	< 0.001
TLA (milliunits)	20	9.5 ± 5.1	20	4.95 ± 3.5	< 0.001
ITLA (milliunits)	20	234 ± 102	20	443 ± 120	< 0.001

inhibitors,[26] kallikrein; d. serum anti-inhibitors of serum pancreatic ferments, e.g. kallikrein inhibitor;[27] e. the enzyme contributions from the salivary gland, the intestinal mucosa, the liver, the oviduct;[16] f. the demonstrated importance of blood steroid levels in the control of enzyme release and their passage through membranes. Indeed a feedback mechanism involving the enzyme, the inhibitor both locally and distantly derived and the anti-inhibitors would comprise a more likely system of regulation of enzyme activity.

That the inhibitors, by and large, are locally derived is amply documented.[24, 28-30] Their secretion into the bloodstream protects the plasma and distant tissues from the noxious activity of free enzyme just as intracellular binding of enzyme prevents autodigestion. In their absence, or due to inappropriate secretion during states of pancreatic inflammation, this autodigestion does take place locally and at distant sites. Indeed, in recovery from inflammation, during repair and pancreatic regeneration, there is evidence of a pancreatic response by increased inhibitor elaboration. Thus, Shaternikov[31] and Chernikova[32] have presented data which indicate that in the rat, during recovery from acute pancreatitis, pancreatic serum trypsin inhibitor may increase 19-fold in the blood. This rising blood enzyme inhibitor content with its

TABLE VI

AVERAGE AMYLASE WHOLE (AWS), DILUTED (ADS) AND ADS/AWS SERUM IN EXPERIMENTS (6 DOGS) WITH INJECTION OF ELASTASE INTO MAIN PANCREATIC DUCT WITH FURTHER LIGATION OF BOTH PANCREATIC DUCTS

Tests	Before operation	After operation				
		2nd day	7th day	14th day	21st day	30th day
AWS						
Mean	620	905	816	790	870	650
SD	244	35	321	188	80	230
n	5	2	4	6	4	4
P	–	> 0.10	> 0.10	> 0.10	> 0.10	> 0.10
ADS						
Mean	1,212	1,380	1,325	990	1,060	590
SD	314	311	666	464	254	229
n	5	2	4	6	4	4
P	–	> 0.10	> 0.10	> 0.10	> 0.10	< 0.05
ADS/AWS						
Mean	2.16	1.53	1.52	1.25	1.23	0.94
SD	1.13	0.43	0.38	0.64	0.35	0.28
n	5	2	4	6	4	4
P	–	> 0.10	> 0.10	> 0.10	< 0.05	< 0.05

resulting decrease in pancreatic ferment activity is capable of releasing the brake to cell division and, thus, initiate repair and regeneration.[33]

The release of pancreatic enzyme inhibitors by the pancreas appears to be regulated by blood steroids. Thus, Faarvang[10, 34] found that the trypsin inhibitor in the α-globulin fraction of the serum is regulated by the steroid hormones and named this inhibitor the "stress and glucocorticoid-regulated" trypsin inhibitor. It would appear that the stress of acute pancreatic inflammation and the response to stress, i.e. increased steroid secretion, may set into motion a cycle of: 1. increased release of pancreatic ferment inhibitors from the pancreas, 2. increased pancreatic ferment inhibitors in the blood, 3. decreased serum pancreatic ferment activity, a cycle of distinct benefit to the organism. Morever, this cycle, according to Vallance-Owen,[34] would release insulin inhibitor initiating or increasing carbohydrate intolerance and diabetes.

The data presented in this report of clinical and experimental studies indicate that pancreatic ferment enzyme inhibitors play a role in determining the level of pancreatic serum enzyme activity in health and disease. The serum ferment inhibitor content appears to be increased in pancreatic inflammatory disease by high protein diets and by the administration of anabolics and corticosteroids. These serum inhibitor levels can be estimated by comparing the enzyme activity of whole serum to diluted serum and from the data calculating an ADS/AWS ratio.

The clinical implications of the study are several. First, it is obvious that technics for determining serum pancreatic ferment activity must be standardized at specific dilutions, lest artifacts of analysis arise and the data from different laboratories be incomparable. Second, the estimation of serum pancreatic ferment activity at two different dilutions and the calculation of a ADS/AWS ratio adds another parameter of pancreatic diagnosis allowing the recognition or confirmation of pancreatic inflammatory disease in patients whose individual serum pancreatic enzyme activities lie with the normal range. Third, the data would support the use of high protein diets, anabolics and glucocorticoids in the treatment of chronic relapsing pancreatitis. The increased serum inhibitor levels, thus induced, as well as the reduced serum pancreatic enzyme activity would be a homeostatic mechanism for the organism. Extrapolating still further, it is possible that the administration of steroids in acute pancreatic inflammation may be of benefit via this mechanism. Finally, the recent use of parenteral alimentation during acute pancreatitis, may in addition to inhibiting pancreatic secretion and maintaining positive protein balance, also increase serum pancreatic inhibitor activity, an additional bonus in therapeutic efficacy.

CONCLUSIONS

The evaluation of serum pancreatic enzyme activity on whole and diluted serum permits the estimation of serum enzyme inhibitor activity via a ADS/AWS ratio. This has diagnostic value in chronic pancreatic disease.

The serum pancreatic ferment activity appears to be regulated in part by serum steroid levels. It is responsive to high protein diet.

A physiologic rationale is presented for the use of steroids and high protein diet in the treatment of acute and chronic pancreatic inflammation.

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Communication from Abroad

Value of B-Scan Ultrasonography in the Diagnosis of Liver Cancer

Accuracy Compared to Scintigraphy and Angiography

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Seventy-one patients with liver cancer were examined by B-scan ultrasonography. The presence of liver cancer was assumed through the irregularity and increased intensity of echos. The accuracy of ultrasonography in the diagnosis of liver cancer was 72%, while the diagnostic accuracy of scintigraphy was 85% and of angiography 93%. No obvious correlation could be demonstrated between the ultrasonographic patterns and serum alpha-fetoprotein (AFP) levels. Ultrasonography is a useful method of detecting liver cancer.

It has been reported that B-scan ultrasonography is a useful technic for the diagnosis of liver diseases, particularly the detection of focal liver diseases such as cysts or abscesses[1-3] as well as for measuring liver volume.[4, 5] It has been suggested that B-scan ultrasonography may serve as a valuable method of diagnosing metastatic tumors of the liver[5-8] but its efficiency in primary liver cancer has not been satisfactorily established. The aim of this study is to assess the usefulness of B-scan ultrasonography in the diagnosis of primary and metastatic tumors of the liver and to compare the diagnostic accuracy of B-scan ultrasonography, scintigraphy and angiography in the same patient.

Materials and Methods

The study population consisted of 119 patients who were selected from admissions to the Kyushu University Hospital from December, 1971 through June, 1976. A total of 71 patients had a surgical or pathologic diagnosis of primary or metastatic liver cancer. Of the thirty-nine patients with primary liver cancer 31 were males and eight were females, whose ages ranged from 43-71 years. The patients with metastatic liver cancer consisted of 22 males and 10 females, whose ages ranged from 41-74

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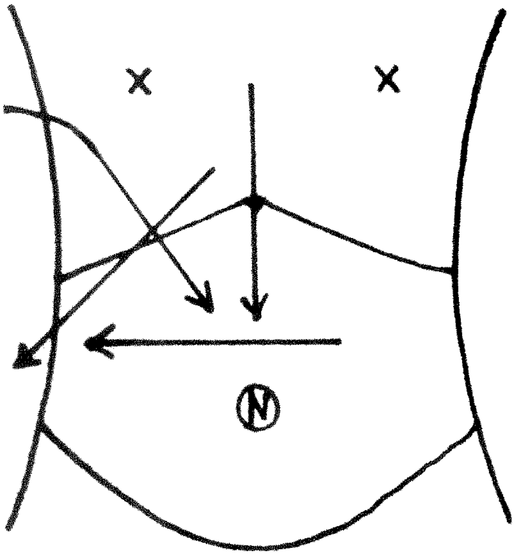

Fig. 1—Routine scanning. Scans at 2 cm. intervals as a rule were obtained in each axis.

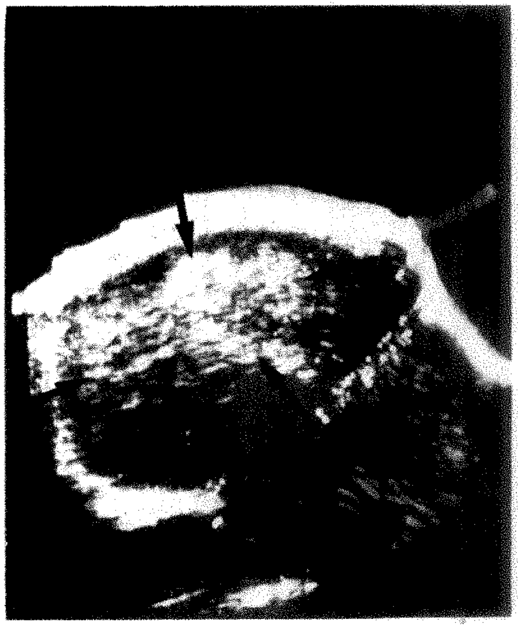

Fig. 3—Solid pattern in the oblique scan.

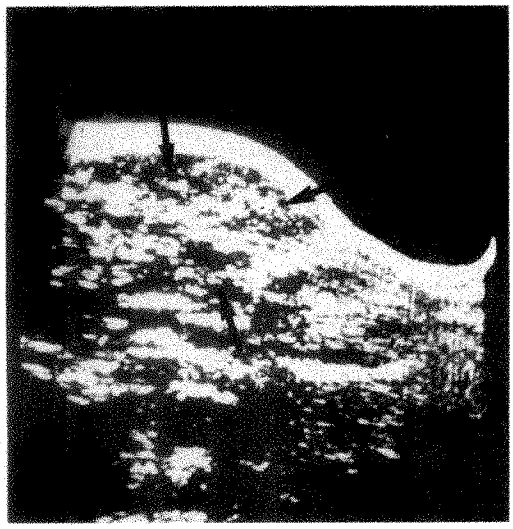

Fig. 2—Diffuse ultrasonographic pattern of primary liver cancer in the longitudinal scan.

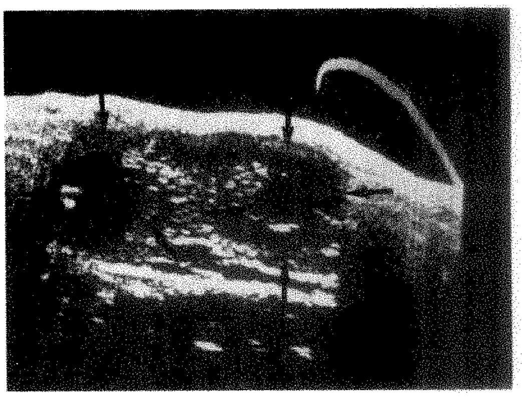

Fig. 4—Cystic pattern in the longitudinal scan.

years. A total of 48 patients with cirrhosis of the liver, diagnosed by appropriate clinical and biochemical criteria and liver biopsy, were also studied. There were 39 males and nine females, ranging in age from 27-69 years. The control group consisted of seven healthy males and five females with normal laboratory values, ranging in age from 26-40 years.

The examination was performed with a Aloka SSD 10C, MSU-6 scanner with a 2.25 MHz transducer of 10 mm. diameter (Aloka, Tokyo, Japan). In the supine position and lying on the left side, the liver was scanned either through an intercostal space or from the subcostal area, as shown in Figure 1. Ultrasonic scanning was performed at intervals of 2 cm. in each axis.

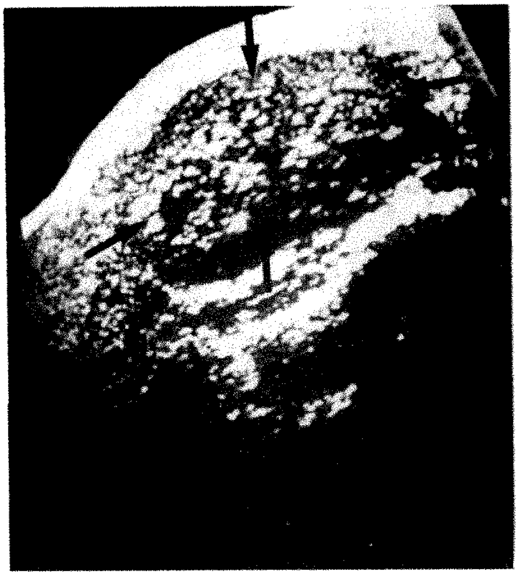

Fig. 5—Mixed pattern in the oblique scan.

The liver was rescanned several times in the same axis with respiration suspended. The transducer was applied manually to the abdomen with the use of olive oil as a coupling agent. The gain-setting value was adjusted until the echo of the inferior surface of the liver was elicited. Ultrasonic scans of the patient were compared with those obtained from a normal subject at the same gain settings. The ultrasonic images of the liver were recorded with a Asahi Pentax camera (Asahi Optical Company, Tokyo, Japan).

Liver scintigraphy was performed using a Shimadzu SCC 150S scanner (Shimadzu, Kyoto, Japan), using either 1.5 millicuries of ^{99m}Tc sulfacolloid, or 200 microcuries of Au^{198}. The distribution of radioactivity on the liver was classified as uniform, patchy, or having single or multiple defects.[9] Selective hepatic angiography was made in 20 patients with primary liver cancer and in seven with metastatic liver cancer, by the Seldinger technic with injections into both the celiac and superior mesenteric artery. Diagnosis of liver cancer by selective hepatic angiography was based on several criteria.[10-15] Serum alpha-fetoprotein (AFP) was tested in the sera of 25 patients with primary liver cancer by a double diffusion in agar and the sera with negative AFP were further tested by an immunoelectroosmophoresis.[16] A quantitation of AFP was done using single radial immunodiffusion incorporating the antiserum in agar[17] and expressed as mg./dl.

TABLE I

RELATIONSHIP BETWEEN ULTRASONOGRAPHIC PATTERNS AND AFP

Ultrasonographic patterns	No. of cases	AFP (mg/dl)
Diffuse	3	29.5 ± 27.0[*]
Solid	13	19.9 ± 43.4
Mixed	8	5.0 ± 7.0
Cystic	1	0

[*] Results are expressed as mean ± SD.

RESULTS

B-scan ultrasonography was performed in 12 normal subjects. The typical scan of the normal liver, at the gain settings which afford the best differentiation from the abnormal liver, shows a liver area with fine and uniformly distributed echos. Liver cirrhosis produces a diffuse increase of coarse echos throughout the liver. We interpreted the presence of liver cancer through the following B-scan ultrasonographic characteristics: 1. irregularity of echos, 2. increased intensity of irregular echos. Retrospective analysis showed that ultrasonographic findings in 25 patients with primary liver cancer could be designated as following four patterns. 1. Diffuse pattern. The irregular echos within the liver appeared diffuse as shown in Figure 2. This group consisted of three patients. 2. Solid pattern. This is illustrated in Figure 3. The solid masses of irregular echos extending

TABLE II

DIAGNOSIS OF LIVER CANCER BY ULTRASONOGRAPHY

Diagnosis	No. of cases	Positive	False positive	False negative	Negative
Primary liver cancer	39	28	–	11	–
Metastatic liver cancer	32	23	–	9	–
Liver cirrhosis	48	–	2	–	46

into the liver area were present in 13 of 25 patients with primary liver cancer. 3. Cystic pattern. Ultrasonography demonstrated a relatively echo-free pattern despite irregular echos as shown in Figure 4. There was only one patient in this series. 4. Mixed pattern. This represented a mixed form with solid and cystic patterns (Fig. 5). This included eight scans in the series.

A quantitative test for AFP was performed in the sera of 25 patients with primary liver cancer, in which the ultrasonographic scans could be grouped into four patterns, using single radial immunodiffusion. As shown in Table I, the three patients with diffuse pattern showed high AFP levels (29.5 ± 27.0 mg./dl., mean ± SD) in comparison to the other groups. The AFP levels in the 13 patients with solid pattern and eight with mixed pattern averaged 19.9 ± 43.4 and 5.0 ± 7.0 mg./dl., respectively, whereas one patient with cystic pattern was AFP negative. No statistically significant difference could be detected, however, between AFP levels among the four groups.

Table II summarizes the results of the accuracy of B-scan ultrasonography in the diagnosis of liver cancer. A positive ultrasonographic diagnosis was obtained in 28 (72%) of the 39 patients with primary liver cancer and 23 (72%) of the 32 with metastatic liver cancer, while false negative results approximate 28% in both groups. It was usually impossible to make a definite distinction between primary and metastatic liver cancer by ultrasonography. Of the 48 patients with liver cirrhosis examined, the total number of false positive results of B-scan ultrasonography was two cases (4%) in which the correct diagnosis was made by either surgery or autopsy.

The frequencies with which abnormalities were detected by ultrasonography, scintigraphy and angiography in patients with liver cancer are shown in Table III. Our studies had a 72% rate of correct diagnosis of primary liver cancer by ultrasonography and 90% by scintigraphy. Two of 28 patients with primary liver cancer detected by ultrasonography were not demonstrated by scintigraphy. Among 11 patients who were not diagnosed as primary liver cancer by ultrasonography, nine were diagnosed by scintigraphy. The combination of both methods yielded a correct diagnosis of primary liver cancer in 37 (95%) of 39 patients examined. A positive angiographic diagnosis of primary liver cancer was obtained in 19 (95%) of 20 patients examined, while there was one false negative diagnosis. The combined accuracy of the three methods was 100% in the 20 patients examined. Of the 32 patients with metastatic liver cancer, ultrasonography and scintigraphy made correct diagnosis in 72 and 78%, respectively. There were seven false negative diagnosis by scintigraphy. The combination of both methods yielded a diagnosis of metastatic

TABLE III

Comparison of Accuracy of Ultrasonography, Scintigraphy and Angiography in Diagnosis of Liver Cancer

Diagnosis	No. of cases	Ultrasonography		Scintigraphy			Angiography	
				Defect	Patchy	Uniform	Positive	Negative
Primary liver cancer	39	Positive	28	26	0	2	14/15	1/15
		Negative	11	9	0	2	5/5	0/5
Metastatic liver cancer	32	Positive	23	21	1	1	2/2	0/2
		Negative	9	4	2	3	4/5	1/5

lesions to the liver in 27 (84%) of the 32 patients examined. A correct diagnosis of metastatic liver cancer by angiography was obtained in six of seven examinations for an accuracy of almost 86%. Although ultrasonography and scintigraphy were good methods of detecting mass lesions in liver cancer, it was usually impossible to differentiate primary from metastatic liver cancer. On the other hand, angiography could differentiate primary from secondary liver cancer in 19 (76%) of 25 patients by angiographic characteristics.

Comment

Hepatic scintigraphy and angiography are established methods of diagnosing liver cancer but the usefulness of hepatic ultrasonography in the diagnosis of liver cancer and the comparative diagnostic value of the three technics in the same patient are poorly understood. Using the method of ultrasonic scanning, McCarthy, et al.[1] have described that the most easily recognizable appearance of metastases or tumor in the liver is either that of a number of ring-shaped masses or of a solid mass within the liver. Our results indicated that 51 (72%) of 71 patients with liver cancer exhibited the combination of both ultrasonographic characteristics as irregular echoes and increased intensity of echos, whereas these appearances were seen in only 4% of 48 patients with liver cirrhosis.

We infer by ultrasonography that there are at least four different patterns of the abnormal echos within the liver in 25 patients with primary liver cancer. Each patient in four categories was followed with serum AFP determination. The Ouchterlony technic and immunoelectroosmophoresis for AFP were positive in 22 of 25 patients with primary liver cancer. In our earlier study,[18] 75 (94%) of the 80 patients with primary liver cancer had elevated AFP levels. In this series, one patient with solid pattern, one with cystic pattern and one with mixed pattern were AFP negative. It has been suggested that the well differentiated hepatomas tend to be of low AFP levels, whereas the poorly differentiated hepatomas tend to be high AFP levels.[19, 20] Our results indicated that AFP production was highest in the histologically intermediate hepatomas.[18] Patients with diffuse or solid pattern were found to have elevations higher than did those with mixed or cystic pattern. No significant differences were found in serum AFP levels, however, between the four groups of ultrasonographic patterns. Further work may be needed to develop the degree of correlation between ultrasonographic patterns and serum AFP levels in patients with primary liver cancer.

Of all patients examined by ultrasonography, there were 11 false negative in primary liver cancer and nine in metastatic liver cancer. In some instances ultrasonography failed to detect liver masses in the hepatoportal area. In addition, it was difficult to detect tumors in the extremely obese patients. It is recently reported that the new gray-scale scanners are helpful in determining the internal ultrasonic properties of solid masses and gray-scale ultrasonic scanning is superior to liver scan, particularly for small lesions.[21, 22] Although ultrasonography in our series was usually carried out in planes at intervals of 2 cm. in the various directions as shown in Figure 1, hepatic lesions smaller than 2 cm. in size were not shown on the scans. Since the resolution of focal lesions by scintigraphy is presently limited to masses of 2 cm.,[23, 24] the ultrasonographic accuracy in detecting liver masses is in agreement with that of scintigraphy.

In the present study a correct diagnosis by scintigraphy was obtained in 35 of 39 patients with primary liver cancer for a 90% diagnostic accuracy and 25 (78%) of 32 with metastatic liver cancer. There were 60 correct diagnoses for an over all diagnostic accuracy of almost 85% and this result was consistent with previous observations in liver cancer,[23, 25] whereas the combination of two or three methods increased the accuracy of diagnosis (Table III). Scintigraphy has shown its value in demonstrating the size and shape of the liver and in detecting space-occupying lesions larger than 2 cm.[23] Diagnosis, however, as to the nature of space-occupying lesion in scintiscan is not possible without clinical correlation.[24, 26]

Hepatic angiography in our series could be more specific as to the nature of liver cancers than scintigraphy and differentiate primary from secondary liver cancer in 19 (76%) of 25 patients by angiographic characteristics.[10-15] The usefulness of ultrasonography and scintigraphy has been analyzed in the accurate diagnosis of focal hepatic lesions.[2, 1] Since scintigraphy is just as accurate in detecting liver masses in general as angiography, angiography following scintigraphy should be performed when the more accurate diagnosis of focal hepatic lesions is needed.[24]

Ultrasonography is a nonivasive technic, different from angiography and performed with no patient discomfort. In fact, ultrasonography is especially valuable for patients with moderate to severe liver disease because the injection of radioisotope or contrast media is unecessary, although it must always be used in conjunction with clinical, x-ray and laboratory data.[27] Moreover, sequential ultrasonographic studies in the same patient are valuable for following the course of liver cancer and monitoring the effectiveness of chemotherapy of liver cancer.

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A Controlled Trial of 6-Methylprednisolone in Acute Alcoholic Hepatitis

WITH A NOTE ON PUBLISHED RESULTS IN ENCEPHALOPATHIC PATIENTS

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In a prospective double-blind study, 27 patients with alcoholic hepatitis were randomized for 6-methylprednisolone (12 patients) or placebo treatment (15 patients). The mortality was 50% among steroid treated patients and 47% in the control group ($P > .05$). The role of liver biopsy feasibility at selection is emphasized since the mortality in this group was 10% as opposed to 71% when the procedure was contraindicated ($P < .01$). Complications in the steroid-treated subjects were similar quantitatively and qualitatively to those observed in the control series.

Examination of published reports of mortality in earlier controlled trials suggests a modest trend in favor of corticosteroid therapy for an encephalopathic subgroup of patients but additional data are required for verification.

INTRODUCTION

Acute alcoholic liver disease is a well-described entity[1-6] with a reported mortality of 4-80%. Within the past several years, several controlled studies have been published on the value of steroids in the treatment of alcoholic hepatitis with conflicting results. Helman, et al[7] reported that prednisolone improved survival in "poor risk", biopsied alcoholic hepatitis patients with hepatic encephalopathy. Porter, et al[8] in a double-blind study of 20 patients with histologic or clinical evidence of alcoholic hepatitis found there was no statistical difference between the steroid (6-methylpred-

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TABLE I

COMPARABILITY OF "BIOPSY FEASIBLE" ALCOHOLIC HEPATITIS PATIENTS

Criteria	Steroid group	Placebo group
No. of patients	4	6
Age (mean)	44 years	46 years
Sex (% males)	75%	50%
Altered mental status*	0%	16%
Liver stigmas	50%	50%
Varices	0%	33%
Bilirubin (mg.%)	9 (6-14)†	16 (2-30)
SGOT u.	168 (100-276)	112 (40-205)
Prolonged prothrombin time	2.1 (1-3.8)	3.3 (2-5.3)
Albumin	2.8 (2.1-3.2)	2.8 (2.1-3.4)
Hematocrit (%)	30 (24-33)	35 (25-39)
WBC (× 10^3/cu. mm.)	15.2 (4.4-25.2)	18.5 (8.3-32.8)

* and/or significant asterixis
† mean (range)

nisolone) and placebo groups in terms of survival, although the survival rates were 45 and 22%, respectively. More recently, Campra[9] and Blitzer[10] have also reported findings which do not demonstrate a significantly improved outcome for steroid-treated alcoholic hepatitis patients.

Significant limitations in the original studies include the small number of subjects and the inclusion of alcoholic hepatitis patients with varying prognosis, since several studies have shown that a prothrombin time that allowed percutaneous liver biopsy preselected patients with an improved prognosis.[4, 11]

In view of the conflicting nature of previously published data, the Boston Interhospital Liver Group, in conjunction with the Emory Gastrointestinal Group, undertook a prospective controlled double-blind investigation of prednisolone treatment in alcoholic hepatitis.

MATERIAL AND METHODS

Patients admitted to the member hospitals with the clinical diagnosis of alcoholic hepatitis, i.e. acute hepatic decompensation associated with acute and chronic alcoholism, were initially screened. The minimal clinical criteria for admission into the study were a history of recent heavy alcoholic ingestion; a serum bilirubin greater than 5 mg.%; hospitalization for at least five days without improvement in liver tests; or rapid deterioration of the clinical condition during a 24-hour period while under observation. In addition, a patient had to have a minimum of two "major criteria" or one "major" and two "minor" criteria" to be placed in the study.

The "major criteria" were a liver biopsy showing alcoholic hepatitis (with or without Mallory bodies), hepatic encephalopathy, azotemia unexplained by another process (BUN greater than 20 mg.% or

TABLE II

COMPARABILITY OF "BIOPSY DISALLOWED" ALCOHOLIC HEPATITIS PATIENTS

Criteria	Steroid group	Placebo group
No. of patients	8	9
Age (mean)	47 years	43 years
% males	25%	44%
Altered mental status*	50%	67%
Liver stigmata	100%	44%
Varices (present by x-ray or endoscopy)	33%	50%
Bilirubin (mg.%)	29.1 (8.5-45)†	20.3 (8.8-46)
SGOT (μ/ml.)	127 (31-202)	180 (51-500)
Prolonged prothrombin time	5.6 (3.4-9)	5.8 (2.7-10)
Albumin (gm.%)	2.2 (1-2.9)	2.3 (1.6-2.9)
Hematocrit (%)	32 (26-42)	32 (21-41)
WBC × 10^3/cu. mm.	20 (10.3-36.9)	20.9 (7.5-43.5)

* and/or significant asterixis
† mean (range)

creatinine greater than 1.5 mg.%, hyperbilirubinemia (greater than 20 mg.%) and prothrombin time prolonged more than four seconds over control and unresponsive to parenteral administration of Vitamin K.

The minor criteria included fever not obviously secondary to another process, WBC greater than 12,000, hepatomegaly (span greater than 14 cm.), splenomegaly, or liver stigmas (spider telangiectasia, palmar erythema, ascites, edema, etc.).

Patients were not considered for the study if their SGOT was greater than 500 but a positive HBAg did not exclude them from the study if a percutaneous liver biopsy confirmed alcoholic hepatitis.

Patients were rejected from the study if they manifested active gastrointestinal bleeding (falling hematocrit, guaiac positive stools, hematemesis), pancreatitis, x-ray evidence of peptic ulcer disease, active or questionably active tuberculosis, acute infection, or severe psychiatric disorder.

Before accepting a patient into the study, a senior and junior staff member had to agree that the minimal criteria had been fulfilled. The patient was then randomized into a predetermined code provided by the drug manufacturer.* Immediately prior to randomization, patients were stratified into two categories based on the presence or absence of criteria permitting hepatic biopsy. The purpose of this procedure was to provide comparable case material for both steroid and placebo control groups. In the absence of other contraindications, patients with prothrombin times less than four seconds prolonged were placed in the "Biopsy-Feasible" (B.F.) group whether or not they agreed to a biopsy. All other patients con-

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* Upjohn Co., Kalamazoo, MI, prepared and supplied the medications and placebo.

TABLE III

Cause of Death of "Biopsy-disallowed" Patients

	Steroid group	Placebo group
Gastrointestinal bleeding	3/6	3/6
Hepatic failure	2/6	—
Acute pancreatitis	1/6	—
Sepsis	—	2/6
Not specified	—	1/6

stituted the "Biopsy-Disallowed" (B.D.) group.

Following randomization, patients were placed on 80 mg. of 6-methylprednisolone or equivalent number of placebo tablets (or parenteral therapy of the same dosage intravenously if gastrointestinal function precluded oral intake) for four to seven days; the medication was then tapered on a flexible schedule with cessation of therapy planned for four weeks unless death or complications intervened. Both groups received comparable supportive care required in hepatic decompensation. All patients with positive tuberculin tests were treated with INH 300 mg. daily and 50 mg. of pyridoxine daily. Informed consent was obtained for all patients.

Twenty-seven patients fulfilled these criteria and were randomized into steroid treatment (12 patients) or placebo (15 patients) categories. Ten patients had percutaneous liver biopsies at selection (B.F. group) and the remaining 17 constituted the B.D. group. No significant differences were noted between steroid treated and placebo treated subjects in either the B.F. or B.D. stratification (Table I and Table II, respectively).

TABLE IV

Complications in "Biopsy-disallowed" Patients

	Steroid group	Placebo group
Encephalopathy*	6/8	6/9
Gastrointestinal bleeding	4/8	5/9
Hepatorenal syndrome	3/8	2/9
Sepsis	2/8	3/9
Diabetic ketoacidosis	1/8	0

* Includes patients with clinical signs at selection.

Clinical evaluation was carried out by junior staff physicians blinded to treatment status of the patients. The following studies were performed on initial presentation (with serial laboratory and clinical determinations repeated prior to randomization and at twice-weekly intervals thereafter): hematocrit, white blood cell count, platelet count, prothrombin time, liver studies, stool guaiac, urine, sputum and blood cultures, tuberculin skin test, chest x-ray and upper gastrointestinal series.

Results

Over all results indicate that the survival rate was 50% (6 of 12 patients) for steroid administration and 53% (8 of 15 patients) for placebo therapy ($P > .05$). One death occurred in the B.F. group (10% fatality rate) in a placebo treated subject due to massively bleeding esophageal varices. A steroid treated patient in the B.F. group voluntarily withdrew from the study after eight days but was retained for statistical purposes. By contrast, of 17 B.D. subjects, five survived for a mortality rate of 71%. Two of eight patients randomized into the steroid group survived

TABLE V

ADRENOCORTICAL STEROIDS IN PATIENTS WITH ALCOHOLIC HEPATITIS AND ENCEPHALOPATHY

Senior author and reference	Control group		Steroid group		
	No. of patients	No. of deaths	No. of patients	No. of deaths	Statistical significance
Helman[7]	6	6	9	1	$P < 0.01$
Porter[8]	8	7	8	6	N.S.
Blitzer[10]	2	1	3	2	N.S.
Campra[9]	10	8	8	4	N.S.
Present study	6	4	6	2	N.S.
Total	32	26	34	15	$P \cong .05$ ($X = 3.88$)

* We are indebted to Dr. Harold Conn of Yale Medical School and to Pergamon Press for permission to reproduce a portion of this material.

while three of nine survived in the placebo group ($P > .05$).

There were no significant differences in the causes of death in the steroid and placebo groups (Table III). Gastrointestinal bleeding terminating fatally accounted for 50% of the mortality in both placebo and steroid treated groups. Hepatic failure, acute pancreatitis and sepsis were the causes of death in the remaining instances. Nonlethal complications were similar in both groups (Table IV) and included hepatic encephalopathy, gastrointestinal bleeding, renal failure, sepsis and diabetic ketoacidosis.

Because of the frequency of side-effects occurring in the B.D. patients which were potentially due to corticosteroids, treatment had to be terminated more frequently in this group than in the B.F. patients. Only three patients remained in the protocol for longer than 21 days (one of eight in the steroid group and two of nine in the control group). The mean duration of treatment of patients on steroids was 8.5 days compared to 16.4 days for those receiving placebo.

COMMENT

The purpose of this study was to examine the value of corticosteroids in the treatment of alcoholic hepatitis. While histological features confirmed the diagnosis in the B.F. group, the clinical criteria established for the B.D. group are relatively specific and it is considered unlikely that patients with other hepatic diagnoses were included in the study. It should also be recognized that the protocol in this clinical trial clearly excluded milder forms of hepatic injury due to alcohol. Since recovery is characteristic in this circumstance, a role for corticosteroids would be more difficult to define.

It is evident that in the two groups defined here, steroids had no effect in altering mortality or morbidity. In the biopsied group, survival does not appear to be the appropriate criterion to evaluate therapy primarily because of an anticipated favorable prognosis.

The nonbiopsied group, as we have defined it, has a 71% mortality rate occurring early in the course of the "treatment phase" of the disease. Although the rate of major complications was similar in both steroid and placebo group, the nature of the complications in simulating the adverse effects of corticosteroids, i.e. gastrointestinal bleeding and sepsis, rendered the use of steroids injudicious.

Whether steroids may reduce tissue injury in alcoholic hepatitis remains unclear. Evaluation of potential histologic improvement cannot be easily achieved when biopsy is medically precluded at treatment onset. Although re-examination of histologic changes was initially planned in the B.F. group, it became impractical largely due to the nature of the patient population. Histologic evaluation of percutaneous liver biopsies following treatment is subject to the limitation of sampling error and the variable of recurrent "toxin" exposure.

The variation in mortality noted in our study has been confirmed by others as reviewed by Porter, et al.[8] Generally, patients in whom there is no contraindication for liver biopsy have a mortality rate below 20%, while those in whom percutaneous liver biopsy is hazardous have reported mortality rates of up to 100%. This suggests that the prothrombin time is the most sensitive laboratory parameter in categorizing the patients into a high or low mortality group. Nevertheless, in the high risk B.D. patients who by definition have prolonged prothrombin time the mean prolongation was nearly identical for survivors (5.7 sec.) and nonsurvivors (5.9 sec.).

Four controlled double-blind prospective studies have now all concluded that there is no evidence that corticosteroids reduce the mortality of severe alcoholic hepatitis. The only study purporting to demonstrate an effect of steroids on reducing the mortality of alcoholic hepatitis[7] involved a small subgroup of 15 encephalopathic patients, all of whom were sufficiently compensated to undergo biopsy. In Table V, we have analyzed the data in all controlled studies pertaining to the survival rate for encephalopathic subjects receiving corticosteroids. The results indicate borderline statistical significance for steroid efficacy. A large multicenter study group would be desirable to reinvestigate this problem with reference to encephalopathy. The quest for a group of patients with moderate severity of illness who might benefit from this therapy[12] remains elusive and ill-defined.

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Communication from Abroad

Metabolism of Bile Acids by Strains of *Acinetobacter Anitratum* and *Acinetobacter Lwoffii*

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The activity of two species of bacteria: *Acinetobacter anitratum* and *Acinetobacter lwoffii,* isolated from jejunum of patients with achlorhydria and Reichel-Polya resection towards bile salts was investigated. These species were not previously tested from this view point. All strains tested hydrolyzed bile salts; conjugates of deoxycholic acid were hydrolyzed more readily than those of cholic acid. This feature may be used as a bacteriological taxonomic criterion.

Bacterial metabolism of bile salts has been extensively studied and demonstrated using a range of species of strictly anaerobic and facultative organisms.[1-4]

In a study of 85 patients with achlorhydria and Reichel-Polya resection we have isolated by protected jejunal intubation 10 strains of *Acinetobacter lwoffii* and four strains of *Acinetobacter anitratum;* carriage of these organisms was associated with clinical steatorrhea and the presence of free bile acids in the jejunal juice.[5] Antibiotic treatment suppressed the bacterial overgrowth, the bile salt metabolism and the steatorrhea. To date there have been no reports of bile salt metabolism by strains of *Acinetobacter anitratum* and *Acinetobacter lwoffii.* This paper reports a study of these strains for their ability to deconjugate bile salts and also to carry out the dehydroxylation of cholic acid to yield deoxycholic acid.

MATERIALS AND METHODS

Bile salts:—The bile salts used (from Maybridge Chemical Company, England) were glycocholic, glycodeoxycholic, taurocholic and taurodeoxycholic acids. Their purity was checked by thin-layer chromatography as described below.

Analytical methods:—Bile acids and salts were analyzed by thin-layer chromatography (TLC) on silica gel G plates (Merck), 0.25 mm. thick, developed with iso-octane:isopropylether:glacial acetic acid:isopropanol (2:1:1:1) and localized by spraying with a 10% ethanolic solution of phosphomolibdenic acid and heating at 115° C for 15 minutes.

Bacterial strains:—The strains tested included four of *Acinetobacter anitratum* (*Bacterium anitratum*) and 10 of *Acinetobacter lwoffii (Mima polymorpha),* identified according to Gilardi's scheme using a complex of morphological and biochemical characteristics.[6, 7] Cultures were maintained on gelose.

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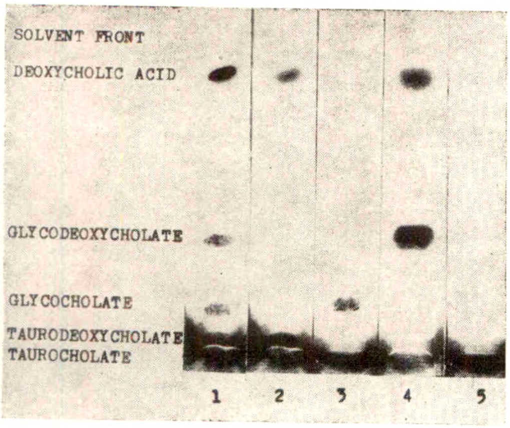

Fig. 1—Thin-layer chromatography of the culture's supernatant (*Acinetobacter lwoffii*). 1. Standard; 2. Taurodeoxycholate; 3. Glycocholate; 4. Glycodeoxycholate; 5. Taurocholate.

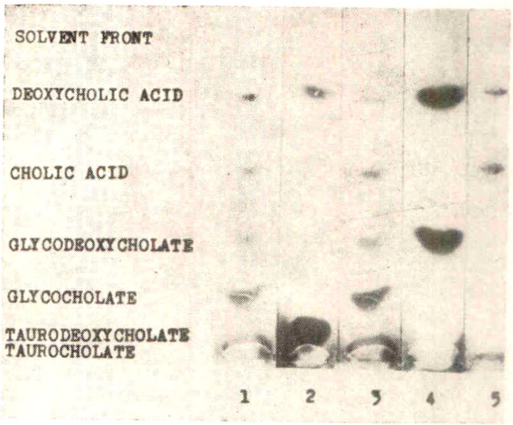

Fig. 2—Thin-layer chromatography of the culture's supernatant (*Acinetobacter lwoffii*—washed and resuspended cells). 1. Standard; 2. Taurodeoxycholate; 3. Glycocholate; 4. Glycodeoxycholate; 5. Taurocholate.
In Column 3 unidentified metabolite with an Rf close to that of glycodeoxycholic acid.

Assay technic:—The organisms were grown in glucose broth containing 0.2% bile salt for 24 hours at 37° C, then 250 microl was applied to a TLC plate and analyzed. In addition washed cell suspension of four strains of *Acinetobacter lwoffii* were assayed. Organisms were grown in glucose broth for 24 hours at 37° C, harvested by centrifugation and resuspended in saline (50 mg. wet weight/m. saline). From this suspension 0.5 ml. was incubated with an equal volume of a 1% solution of bile salt for 24 hours at 37° C, then analyzed by TLC.

Results

All four strains of *Acinetobacter anitratum* hydrolyzed all four bile salts. The conjugates of deoxycholic acid were hydrolyzed more readily than those of cholic acid; taurine and glycine conjugates were hydrolyzed equally readily.

Similarly, all 10 strains of *Acinetobacter lwoffii* hydrolyzed conjugates of deoxycholic acid. Only six of 10 strains were also able to hydrolyze cholic acid conjugates. The hydrolysis was accompanied by 7-alpha-dehydroxylation of the released cholic acid to yield deoxycholic acid. The remaining four strains were inactive against cholic acid substrates (Fig. 1).

These four strains were therefore assayed as washed cell suspensions. Under these conditions they hydrolyzed all four substrates; further an unidentified metabolite (with an Rf close to that of glycodeoxycholic acid) was produced from glycocholic acid (Fig. 2).

Comment

There have been no reports in the literature on the metabolism of bile salts by *Acinetobacter anitratum* and *Acinetobacter lwoffii*, although this reaction has been extensively investigated with other organisms[8-12] beginning with Norman's and Bergstrom's research.[13, 14]. In 1965, Kalser, et al isolated some bacterial species belonging to the genus *Herellea* (*Acinetobacter*) from the human small intestine[15] but their behavior against bile salts was not described. The two species described in this paper were present in high numbers

(10^6-10^8 organisms/ml.) in the jejunum of patients with achlorhydria and Reichel-Polya resection.[5, 16] They were always associated with the presence of free bile acids in the jejunal juice and with clinical steatorrhea. Oral antibiotic therapy suppressed the bacterial growth and steatorrhea and normalized the bile salt metabolism in the jejunum.[16] The results reported in this paper are therefore consistent with the clinical findings.

All of the 14 strains were more active against deoxycholic acid conjugates than against those of cholic acid. Indeed, four strains of *Acinetobacter lwoffii* showed no activity against cholic acid conjugates in growing cultures, although washed cell suspensions were active. Possibly the growing culture assay system tests only the enzyme activity in the culture supernatant and in these strains the enzyme active on cholic acid conjugates is strongly cell-bound.

Since all 14 strains were active in bile salt hydrolysis we suggest that this characteristic be tested as a possible taxonomic criterion, since to date there have been no reports of other gram-negative nonspore-forming aerobic organisms (such as enterobacteria) carrying out this reaction.

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Vibriocidal Antibody Titer Rise After Rectal or Anal Administration of *Vibrio Cholerae* in Dogs

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In many developing countries anal ablution with surface water is a daily habit. This water is heavily contaminated with microbes, raising the possibility that anal contamination may lead to immune responses. This hypothesis was experimentally tested in 21 dogs by anal or rectal application of *Vibrio cholerae* suspension. *V. cholerae* was recovered from rectal swab cultures for a mean of one day after rectal contamination and 2.5 days after anal application ($P < .02$). Significant increases occurred in the geometric mean titer of serum vibriocidal antibody; this suggests the need for study of the possible role of anal ablution in maintaining serum vibriocidal antibody levels in endemic cholera areas.

INTRODUCTION

In many developing countries it is customary to wash or immerse the anal area in surface water after defecation.[1-3] The water used for this purpose usually contains many microbes, including pathogenic bacteria. The possible significance of this habit in regard to pathogenesis or immune status has not been studied in man but in birds aboral contact with environmental antigens stimulates immune responses[4] and the vent has long been used in veterinary medicine to immunize fowl using live laryngotracheitis virus.[5] If mammals also respond immunologically to aboral contact with pathogens, then anal contamination might lead to immune responses and increased herd immunity. To test this hypothesis experimentally, the serologic response to anal and rectal contamination with *Vibrio cholerae* was studied in dogs.

MATERIALS AND METHODS

Adult Bangladesh pariah dogs were fasted overnight and anesthetized with 20 mg./kg. of intravenous sodium pentobarbital. After performing a venipuncture to obtain blood for serum antibody, and obtaining a rectal swab for culture, a 500 ml. saline enema (150 mmol/l. NaCl) was given, and then vibrios were administered by one of three procedures, described as follows. In *Procedure A*, 50 ml. of 12-hour unshaken broth culture of *V. cholerae* Inaba 569B (a laboratory strain originally obtained from a cholera patient) was given to seven dogs via sterile catheter advanced 5 cm. into the rectum. The inoculum contained 10^{10} cells grown in 1% trypticase 1% NaCl medium.[6] In *Procedure B*, seven other dogs received (by the same route) 100 ml. of 12-hour unshaken alkaline (pH 8) 1% peptone water cholera culture of the same organism (2×10^9 cells) plus 100 ml. Syncase medium.[7] The strain and the inoculum procedures used were chosen because they are known to induce cholera in dogs when delivered into the small bowel.[8] In *Procedure C*, 1 ml. of *V. cholerae*

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TABLE I

DAYS OF POSITIVE CULTURE AFTER DAY OF PROCEDURE ($\bar{x} \pm$ S.E.M.)

Procedure	Day of procedure			
	1	11	34	45
A	1.3 ± 0.3	—	1.1 ± 0.3	—
B	1.0 ± 0.2	0.9 ± 0.3	—	—
C	2.3 ± 0.4	1.3 ± 0.4	—	2.6 ± 0.2

Mean number of days on which rectal swab cultures were positive, starting after the day on which procedures A, B or C were performed (Range of positivity 0-5 days). Each number represents the mean duration of positive cultures of seven dogs.

suspension (2×10^9 cells) grown in the alkaline peptone water medium was applied in droplets to the external anal epithelium of seven additional dogs. Vibrio suspension was drawn inwards during anal contraction and relaxation, thereby contacting the mucosa.

Dogs regained consciousness in metabolic cages in which feces passed through a grill to trays beyond reach of the animals. Water was always available but food was given starting 24 hours after the procedures and was removed if not promptly consumed. Due to the period of fasting, defecation was usually delayed until the third day after the procedures, by which time rectal swab cultures were usually negative for *V. cholerae* (Table I). Cages were frequently checked and cleaned to prevent coprophagy, which was not seen to occur.

Additional rectal swab cultures were obtained immediately after the procedure and then daily, until two consecutive cultures showed no *V. cholerae*. Tellurite-impregnated swabs were dipped in alkaline bile-peptone enrichment medium before swabbing. Cultures were plated on selective thio-sulphate citrate bile salts agar[9] (TCBS) directly and also after six and 18 hours incubation at 37° C in alkaline bilepeptone water enrichment medium. Procedure A was repeated after 34 days and procedures B and C were repeated after 11 days. Procedure C (anal application) was again repeated at 45 days (Table I).

Sera were obtained from blood collected by venipuncture at intervals after the procedure (Fig. 1). Inaba and Ogawa vibriocidal titers of serial serum dilutions, starting with 1:20 diluted serum, were measured in triplicate by a standard method developed at the laboratory.[10] All specimens were titered simultaneously on three occasions. Antitoxin was measured by a passive hemagglutination method.[11]

RESULTS

Initial rectal swabs were vibrio-negative but *V. cholerae*, confirmed by agglutination with type-specific sera, was recovered from all cultures taken after the experimental procedures and from cultures taken one to three days later in most dogs, and five days later in one dog (Table I). Vibrios were recovered longer after anal application than after rectal administration ($P < 0.02$, Table I). Duration of positive culture did not change significantly when the procedures were repeated. No animal developed diarrhea. One dog (Procedure B) died of nondiarrheal causes after two weeks.

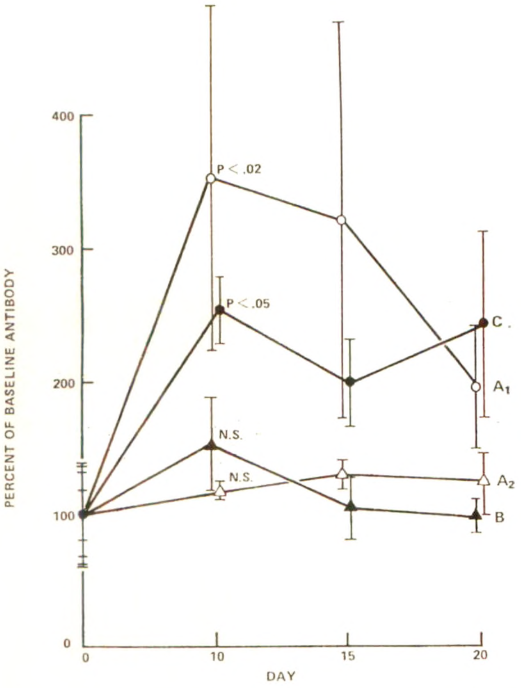

Fig. 1—Reciprocal geometric mean of triplicate serum titers of vibriocidal antibody of dogs demonstrating a threefold or greater antibody titer after rectal or anal vibrio inoculation.

Significant vibriocidal activity was present in dilutions of most initial sera. Average base line geometric mean serum vibriocidal titers (expressed as reciprocal serum dilutions showing activity) were 136 (Inaba; range:40-420) and 446 (Ogawa: range:40-2560). These base line titers probably reflect nonspecific cross-reacting antibody, since similar titers occur in United States dogs.[12]

Geometric mean Inaba vibriocidal antibody titers rose significantly in groups A (first challenge) and C by the tenth day after Procedures A and C and declined thereafter (Fig. 1). No significant rise occurred when Procedure A was repeated after 34 days. Serum antitoxin was measured after Procedure A and showed no change; therefore, the test was not repeated in the remaining dogs.

COMMENT

The findings that aboral contact with *V. cholerae*, while incapable of causing canine cholera, produces a serum antibody response, suggests the possibility that environmental pathogens may induce immune responses after contact with anal or rectal mucosal immunocytes, and offers a possible mechanism for maintenance of vibriocidal titers in endemic areas.

In human volunteers, no infections or vibriocidal titer changes developed after ingestion of up to 10^8 live *V. cholerae* organisms without prior neutralization of the highly vibriocidal gastric acid.[13-14] Since surface water *V. cholerae* counts in endemic areas are very low, ingestion even of several liters of water daily would be unlikely to provide enough *V. cholerae* to generate an immune response.

Clinical infection rates and immune responses increase when gastric acid is absent or is neutralized with $NaHCO_3$,[13-15] and hypochlorhydria does exist in endemic cholera areas[16] but seems unlikely to account for the vibriocidal titer rises observed there annually in 27% of children.[17-18] Since most individuals are normochlorhydric,[19] it is not easy to explain how oral ingestion of *V. cholerae* alone can entirely account for the maintenance of significant vibriocidal titers by 90% of the population by the age of puberty.[17-18] Contact between *V. cholerae* and the anal mucosa by-passes the vibriocidal gastric acid barrier, so that surface water *V. cholerae* counts would appear more likely to induce a vibriocidal titer rise after aboral contact than after oral ingestion. This suggests the need for field study of the relative importance of oral and aboral routes in the maintenance of antibody titers against *V. cholerae*.

The short period of recovery of vibrios after rectal inoculation may be due to the effects of competing microbial flora on vibrio survival in the rectum. The survival of vibrios for several days after anal application is of interest, because it suggests that the surveillance practice of intensive rectal swab field surveys for inapparent infections[20] may sometimes detect anorectal contamination rather than actual infection. This possibility is consistent with a report that no vibrios could be detected in stools after purging of 46% of individuals from whom a positive rectal swab culture for *V. cholerae* had been obtained.[21]

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Barrett's Esophagus

Clinical Review of 26 Cases

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Barrett's esophagus was diagnosed in 26 men in a five-year period by demonstrating esophageal specialized columnar epithelium in target biopsies obtained at endoscopy or in peroral suction biopsies of the esophageal mucosa. The clinical, radiologic and manometric features of these patients were reviewed retrospectively. Esophageal lesions associated with this epithelium included distal and midesophageal strictures and ulcers, alone or in combination, or simply esophagitis. One patient had an associated adenocarcinoma. Twenty of 26 (77%) had heartburn or regurgitation, 16 (62%) had easily elicited reflux of barium while supine and 16 of 17 tested had lower esophageal sphincter pressure in the incompetent range. Ninety-six percent had one or more of these parameters positive. This series demonstrates a wide spectrum of esophageal lesions in Barrett's esophagus, and supports the concept that this lesion occurs as a consequence of gastroesophageal reflux and erosive esophagitis. The case of adenocarcinoma in this series adds to the concern that the columnar lined lower esophagus may be a premalignant lesion.

INTRODUCTION

In 1970 Trier established strict histological criteria for the specialized columnar epithelium found in Barrett's esophagus.[1] From 1971 through 1975, we made a careful search of esophageal mucosal biopsies submitted for histologic diagnosis by the gastroenterology residents in our hospital. Esophageal biopsies from 26 patients conformed to the histologic criteria of Trier and in a retrospective manner the clinical findings were assessed and form the basis of this report. The radiologic findings from these cases are presented in greater detail in a separate report.[2]

METHODS

Twenty-six patients seen on the Medical Service of the Boston Veterans Administration Hospital were diagnosed as having Barrett's esophagus by establishing the presence of a specialized columnar epithelium lining the lower esophagus.[1] Following this histologic identification, the clinical, radiological, endoscopic and manometric data were collected and analyzed retrospectively. As part of their clinical evaluations, the patients had been studied with barium contrast radiological examina-

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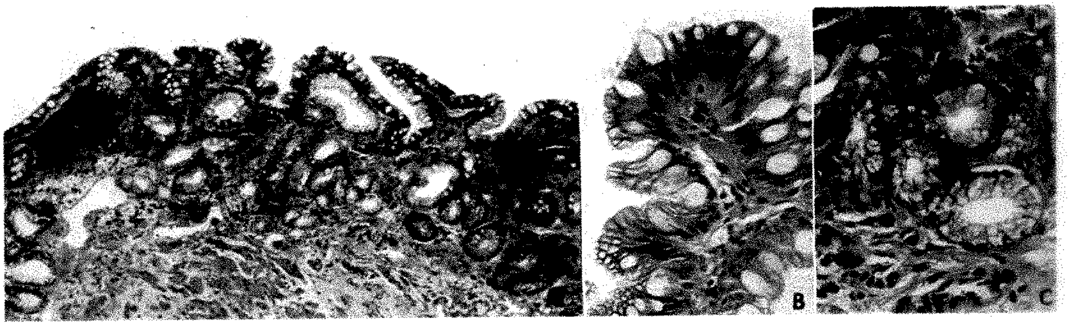

Fig. 1A Fig. 1B Fig. 1C

Fig. 1—Photomicrographs of a peroral suction-biopsy of esophageal mucosa from Case 19 showing specialized columnar epithelium. The biopsy was obtained from the body of the esophagus distal to the mid esophageal stricture and ulcer. A. Low magnification showing villous-like folds and deep glandular pattern (hemotoxylin and eosin, original magnification x40). B. High magnification of surface epithelium showing mucus-secreting columnar epithelium interspersed with typical goblet cells (Hematoxylin and eosin, original magnification x200). C. High magnification of glandular area showing mucus cells. Parietal or chief cells were not seen in the glands (Hematoxylin and eosin, original magnification x200).

tions of the upper gastrointestinal tract, esophagogastroscopy using an Olympus end-viewing fiberoptic endoscope and cytological examinations. Seventeen patients had esophageal manometry using a triple lumen catheter system (tubes 1.4 mm. in internal diameter) perfused with water (1.2 ml./min.) with intraluminal pressures transmitted to Sanborn 267A external transducers. Pressures were recorded in mm. Hg. with the mean gastric fundic pressure used as the zero reference point.[3]

Twenty-three of 26 patients had target biopsies of the esophageal mucosa obtained under direct vision at endoscopy. In 20 patients an additional 65 biopsies were obtained from the esophagus and proximal stomach serially at measured distances from the teeth using a multipurpose suction biopsy tube (Rubin tube).[4] The biopsies were fixed in either formalin or Bouin's solution, embedded in paraffin and sectioned serially at 4-6μ. Sections were stained with hematoxylin and eosin. Histological preparation of some of the peroral biopsies was kindly performed by Dr. Jerry E. Trier, then at the Boston University Medical Center.

Histologic criteria:—The biopsies diagnosed as specialized columnar epithelium had the following morphologic features when examined with the light microscope: 1. villous-like folds or projections into the esophageal lumen; 2. a lumenal surface lined by columnar epithelial cells, the apices of which contained mucous secretory granules; 3. intestinal type goblet cells interspersed among the surface epithelial cells and 4. mucosal glands containing mucous cells and goblet cells[1] (Figs. 1A, 1B and 1C).

Paull, et al have recently expanded the histological criteria for Barrett's esophagus by documenting that some patients with mid esophageal strictures have, in addition to specialized columnar epithelium, gastric fundic-type and junctional-type epithelium occurring above the lower esophageal sphincter (LES).[5] In our cases biopsies were taken in a clinical setting, either under direct vision or with the Rubin tube at measured distances from the incisor teeth; biopsies were not taken with simultaneous localization of the LES. Thus, patients in whom we found only junctional-type or gastric fundic-type epithelium were not in-

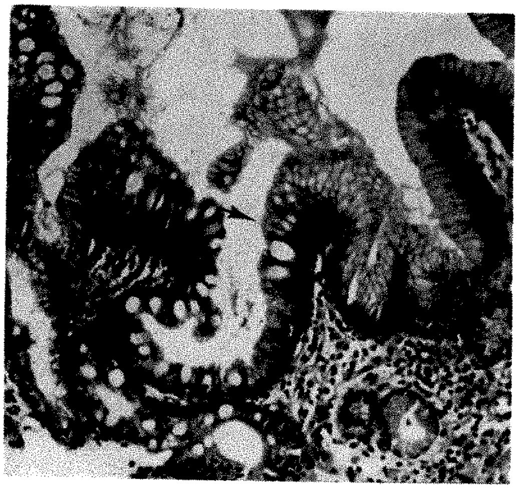

Fig. 2—Photomicrographs of punch biopsy obtained from the distal esophagus from Case 18. This section demonstrates a junction between specialized columnar epithelium (to left of arrow) and junctional-type epithelium (Hematoxylin and eosin, original magnification x100).

cluded in this case review, as it was not certain whether the biopsies had been actually taken from the distal esophagus or had been taken from the gastroesophageal junction or gastric fundus. Biopsies from two of our patients (taken at 35 cm. from the incisor teeth), straddled a border of specialized columnar epithelium and junctional-type epithelium, clearly demonstrating their distinguishing histological features (Fig. 2).

RESULTS

A summary of pertinent findings for the 26 patients are presented in Tables I and II.

Clinical features:—Dysphagia for solids was the presenting complaint in 21 patients, and was accompanied by odynophagia in four. Twelve patients had dysphagia for less than six months, whereas in nine dysphagia and esophageal strictures occurred from one to 20 years prior to our diagnosis of Barrett's esophagus. Three patients (Cases 5, 8, 15) had had previous surgical repairs of hiatal hernias. Eighteen patients reported heartburn, four judged to be a severe and daily symptom and 13 as a moderate and less frequent symptom. Eleven patients had frequent or occasional regurgitation of food or liquid. In summation, 20 patients had definite heartburn, regurgitation, or both, whereas six reported neither symptom.

Two patients, Cases 1 and 4, developed esophageal strictures while in the hospital, demonstrated by serial barium swallow and endoscopic examinations over periods of 12 and 43 days. Both patients had prolonged nasogastric intubation early in their hospital courses, and both developed severe hemorrhagic esophagitis and very narrow distal strictures. It is not known in either case whether the columnar-lined lower esophagus was present before the hemorrhagic esophagitis or developed subsequent to it.

Radiological features:—Esophageal strictures and ulcers, either in combination or alone, were the principal radiologic findings (Table I). Twenty-one patients had strictures, seven in the mid esophagus and 14 in the distal esophagus. Fourteen patients had distinct esophageal ulcers: four in association with mid esophageal strictures, eight with distal strictures (Fig. 3) and two without concomitant strictures. Eighteen patients had mucosal irregularity or nodularity in the distal esophagus that suggested superficial ulcerations or inflammatory changes.

Hiatal hernias were detected in 20 patients, and easily demonstrated gastroesophageal reflux of barium while in the supine position (with neither abdominal compression nor water siphon) occurred in 16. Seven patients, six of whom had distal esophageal strictures, had radiological evidence of duodenal ulcer disease, and one patient had an antral ulcer.

TABLE I

Clinical and Radiologic Features in 26 Men with Barrett's Esophagus

			Clinical*			Radiologic				
Case #	Age (yr.)	Alcohol abuse	Dysphagia (duration-yr.)	Wt. loss (4.5 kg.)	Other	Location	Stricture	Ulcer	Mucosal abnormality**	Other
1	38	+	+ (½)	+	NG intub. hematemesis, odynophagia	distal	+	—	+	
2	52	—	—	—	abd. pain, vomiting	distal	+	—	+	
3	61	+	+ (½)	—		distal	+	—	+	
4	49	—	+ (½)	—	NG intub. hematemesis	distal	+	—	+	duod. ulcer
5	55	?	+ (3)	+		distal	+	—	—	duod. ulcer
6	64	?	+ (½)	+		distal	+	+	—	
7	53	+	+ (½)	—		distal	+	+	+	duod. ulcer
8	68	+	+ (2)	—		distal	+	+	—	duod. ulcer
9	76	—	+ (½)	—	odynophagia	distal	+	+	—	duod. ulcer
10	50	+	+ (½)	—		distal	+	+	—	
11	64	+	+ (2)	+	odynophagia	distal	+	+	+	
12	86	—	+ (1)	+		distal	+	+	—	duod. ulcer
13	52	+	—	—	hematemesis	distal	+	+	+	
14	50	+	+ (½)	—		mid-	+	—	+	
15	57	—	+ (5)	+		mid-	+	—	—	
16	44	—	+ (20)	+		mid-	+	—	+	
17	52	+	+ (8)	+	odynophagia	mid-	+	+	—	
18	42	+	+ (½)	—		mid-	+	+	+	
19	66	+	+ (1)	+		mid-	+	+	+	
20	58	?	+ (½)	—		mid-	+	+		
21	62	+	—	—	pneumonia		—	+	+	
22	55	—	—	—	hematemesis		—	+	+	duod. ulcer
23	45	—	+ (½)	—			—	—	+	
24	53	+	+ (4)	—			—	—	+	
25	59	+	—	—	hematemesis		—	—	+	gastric ulcer
26	50	+	+ (½)	+	odynophagia	distal‡	+	—	+	

+ present
— absent
? unknown
* excluding heartburn and regurgitation (Table II)
** diffuse distortion, nodularity, irregularity or thickening
‡ adenocarcinoma

NG intub: prior nasogastric intubation
distal: contiguous to gastroesophageal junction
mid-: middle third of esophagus, separate from gastroesophageal junction

TABLE II

ASSESSMENT OF REFLUX PARAMETERS IN 26 PATIENTS WITH BARRETT'S ESOPHAGUS

Case	Historical		Radiologic		Endoscopic-histologic	Manometric
	Heartburn (− to ++)*	Regurgitation (− to ++)*	Hiatus hernia	Barium reflux	Esophagitis (− to ++)**	LES pressure (mm. Hg.)
1	+	+	+	+	++	3-10
2	−	+	+	+	+	ND
3	+	−	+	+	+	ND
4	−	−	−	−	++	ND
5	+	+	+	+	+	3-5
6	+	−	+	−	+	2-4‡
7	++	++	+	+	++	ND
8	−	−	+	+	++	ND
9	++	−	+	−	+	5-8
10	+	−	+	−	+	5-8
11	−	+	+	+	++	2-3
12	−	−	+	+	++	ND
13	−	−	+	+	+	2-7
14	+	+	+	+	++	3-6
15	+	−	−	−	−	3-6
16	−	−	−	+	+	3-6
17	++	+	−	−	−	5-8
18	+	+	+	+	+	5-7
19	++	+	+	+	+	3-7
20	+	−	+	−	+	ND
21	−	−	+	+	++	3-10‡
22	+	−	+	−	++	2-5
23	+	−	+	−	+	3-10
24	+	−	+	+	++	3-6
25	+	−	−	−	+	9-17
26	+	+	+	−	−	ND
Total positive	18	11	21	16	23	16/17

*
++ symptom occurs daily
+ symptom occurs less than daily
− symptom does not occur
ND + not done

**
++ purulent exudates
+ erythemea, friability; polymorphonuclear leucocytes in biopsies;
− no inflammation

‡ nonspecific motility disorder (see text)

Endoscopic features:—The findings at endoscopy correlated closely with the x-rays. Nineteen patients had strictures located 20-40 cm. from the incisor teeth. In two cases where radiographic narrowing was noted on barium swallow, no stricture was noted at endoscopy. These patients had deep ulcers on the distal esophagus in areas of severe esophagitis. Only nine of 14 radiologically detected ulcers were seen at endoscopy, due to the inability to pass the endoscope into the associated stricture. Esophagitis was present in 22 patients, varying in severity from the occurrence of erythema and moderate friability (12 patients) to purulent exudates and multiple superficial ulcerations (10 patients) (Table II). In Cases 25 and 26, junctions in the mid esophagus between squamous epithelium (light pink in color) and columnar epithelium (deeper pink) were apparent to the endoscopist.

Histologic features:—The histologic features diagnostic of esophageal specialized columnar epithelium are described under Methods. Positive biopsies were found from 20-35 cm. from the incisor teeth.

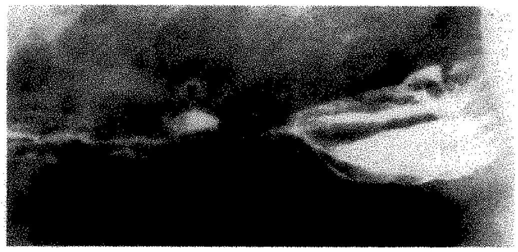

Fig. 3—Barium swallow examination from Case 9. Mucosal views of the distal esophagus show an angular ulceration measuring 15 × 7 mm. (arrows). A hiatus hernia is also visible. Free gastroesophageal reflux was noted fluoroscopically.

Typically, the proximal extent of the specialized columnar epithelium was either at or just below the level of the strictures and ulcers, with inflammatory or granulation tissue at these lesions separating proximal squamous epithelium from distal columnar epithelium. To the best of our knowledge, the columnar lining was continuous in its distribution from its proximal margin to the gastroesophageal junction.[5] Polymorphonuclear leucocytes commonly were found within both squamous and columnar epithelia and the degree of inflammation in the biopsies generally corresponded to the degree of esophagitis noted at endoscopy (subjective evaluations). Those patients with distal esophageal lesions (Cases 1-13, 21-25) appeared to have more severe esophagitis at endoscopy and by biopsy than did patients with mid esophageal strictures (Table II).

Manometric features:—Seventeen patients had manometric studies of the esophagus. Using LES pressures of less than 10 mm. Hg. as the criteria for sphincter incompetence, 16 of 17 were incompetent.[3] One patient had a LES pressure of 9-17 mm. Hg. Two patients had nonspecific motility disorders in the body of the esophagus, characterized by postswallowing increases in pressure which were peristaltic but which were of decreased amplitude and duration. Upper esophageal sphincter and pharyngeal function were normal in all patients.

Therapy and course:—The long-term treatment and the clinical courses of patients in this series, in regard both to the progression of their benign lesions and to the possible development of malignant lesions in Barrett's esophagus will be dealt with in subsequent studies. In brief, initial therapy included antacids, elevation of the head of the bed and bouginage of strictures. Eight patients have required repeated bouginage at intervals from three days to four months, four patients have had surgical repairs of hiatal hernias with fundoplications, and one patient had resection of a stricture. The patient with adenocarcinoma underwent partial esophagectomy and esophagogastrotomy but died of recurrent disease 18 months after presentation.

COMMENT

The 26 patients with Barrett's esophagus presented in this series demonstrate a variety of radiologic and endoscopic lesions. These included not only the midesophageal strictures and esophageal ulcers characteristically described in Barrett's esophagus but also distal strictures and, simply, distal esophagitis. Since dysphagia was the principal complaint in 21 patients, the high number of strictures may actually overestimate the frequency of strictures in patients with Barrett's esophagus. Indeed, in the two patients who developed strictures in the hospital, prolonged nasogastric intubation may have accelerated stricture formation. Additionally, as in Cases 23, 24 and 25, specialized columnar epithelium may occur with only esophagitis in patients whose only symptoms many be heartburn or regurgitation. Nevertheless, the data from our patients and from those in other series, indicate that most patients with Barrett's esophagus have esophageal lesions that are associated with severe erosive esophagitis.[6-10]

The concept that Barrett's epithelium develops as a consequence of acid-peptic reflux is supported by the data in this retrospect study. Twenty of 26 patients (77%) had heartburn, regurgitation or both, 16 of 26 (62%) had easily elicitable gastroesophageal reflux of barium while supine and 16 of the 17 tested (94%) had a manometrically documented incompetent LES. In total, 25 of 26 (96%) had at least one of these manifestations commonly associated with gastroesophageal reflux. The parameters used to diagnose gastroesophageal reflux in our patients are relatively insensitive when compared to direct measurement of intralumenal esophageal pH.[11, 12] These tests are usually positive, however, when unequivocal and consequential reflux occurs[12] and LES pressure is clearly an important determinant of gastroesophageal reflux.[13]

In our retrospective case analysis, we have not determined whether patients with Barrett's esophagus have more severe reflux than do other patients with reflux esophagitis, nor whether our patients have significant nocturnal reflux while supine, a factor that may be important in the development of esophagitis.[14] Additionally, we have not explored the possibility that acute inflammation has lowered LES pressure in these patients, an interesting experimental observation that has been made in cats.[15] Moreover, since some patients with Barrett's esophagus have gastric fundic-type epithelium above the LES, acid-peptic secretion in those cases may initiate or enhance esophagitis.[5, 16, 17]

Paull, et al,[5] in their careful histological study have documented the histological spectrum of esophageal columnar epithelium in Barrett's esophagus, greatly clarifying previous controversy in this area. Specialized columnar epithelium, which we utilized for our diagnoses, was found distal to mid esophageal strictures in nine of 12 of Paull's patients and always occurred proximal to the other types of columnar epithelium found in the esophagus. Therefore, endoscopic biopsies obtained within or just distal to strictures and ulcers usually will contain specialized columnar epithelium and will confirm readily the diagnoses of Barrett's esophagus.

The origin or mode of development of Barrett's epithelium is not known. Bremner, et al,[18] based on studies of experimental reflux in dogs, postulate that proximal migration or "creeping substitution" of junctional epithelium into areas of erosive esophagitis is the mechanism for the columnar-lined lower esophagus. Adler and co-workers, from a clinicopathological study of 11 patients[8] and from a large autopsy series,[19] suggest that Barrett's epithelium originates from superficial mucous glands found in the *lamina propria* of the esophagus, which replace eroded squamous epithelium. More recently, Hamilton and Yardley have demonstrated the development of cardiac-type epithelium and in some cases specialized columnar epithelium, in the distal esophagus of patients with esophagogastrostomies and marked reflux.[20] Thus with acid-peptic reflux and erosion of esophageal squamous epithelium, several types of columnar epithelium may develop, perhaps regenerating from different origins (gastric cardia or esophageal submucosal glands), and perhaps with the potential to change histologically.

The frequency of alcohol abuse in this series (15 of 23) is high but is not necessarily unusual for middle-aged veteran men admitted to our hospital. The prevalence of alcohol abuse for patients with Barrett's esophagus has not been reported in other series. We have collected a large number of cases of Barrett's esophagus in a five-year period in a hospital which treats many alcoholics and we have continued to diagnose Barrett's esophagus in alcoholic men. Thus, it is only speculative that alcoholism may contribute to the pathogenesis of this lesion, perhaps doing so by adversely affecting LES pressure or esophageal motility,[21] or by enhancing the development of esophageal erosions.

Esophageal adenocarcinoma occurs in Barrett's esophagus and it has been suggested that the columnar-lined lower esophagus may be a premalignant lesion.[22-25] Indeed, Naef, et al's large retrospective series indicates a prevalence of adenocarcinoma arising within the columnar lined esophagus of close to 10%.[25] Of clinical importance is that in Case 26, the malignant stricture was located near the gastroesophageal junction, 10 cm. below the squamo-columnar junction in the mid esophagus. Thus, the suspicion for malignancy must be very high when strictures arise within esophageal columnar epithelium. It is not known, however, whether patients with Barrett's esophagus actually do have a greater risk for carcinoma than other patients with reflux esophagitis.

Despite the distinctive histologic appearance of specialized esophageal columnar epithelium, the results from our retrospective review indicate that Barrett's esophagus perhaps best be considered as part of the spectrum of reflux esophagitis rather than as a separate clinical entity. Certainly, treatment of these patients, whether medical or surgical, is directed against acidpeptic reflux. Why some patients with reflux develop this columnar epithelium, where it originates, and whether it indeed represents a premalignant lesion, are questions yet to be answered.

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Clinical Vignette

Mucoepidermoid Carcinoma of the Esophagus

REPORT OF AN UNOPERATED AUTOPSY CASE AND REVIEW OF LITERATURE

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The esophageal tumor which occurred in a 53-year old female and was histologically similar to the salivary mucoepidermoid carcinoma, showed local invasion at autopsy. No distant metastasis was noted. Our literature review showed invasive and metastatic nature of the tumor. Submucosal location of the tumor in our case supported the proposed origin of the neoplasm from the esophageal gland.

Despite the relatively frequent occurrence of mucoepidermoid carcinoma in the major and minor salivary glands,[1] its occurrence in the esophagus has been reported on only a few occasions.[2-6] In seven previously reported cases, postmortem examination was performed on two cases and the tumor shown to be locally invasive,[4] or widely metastatic.[2, 5] From the reported cases in the literature, postoperative survival time varied from two days to 14 years and it has been considered very difficult to predict the prognosis of this tumor.

We recently had an opportunity to perform an autopsy on a case of unoperated mucoepidermoid carcinoma of the esophagus which occurred in a 53-year old Japanese female. Our present report is aimed at contributing an additional case to the sparse literature and brief clinicopathological review of the previously reported cases. This was the third reported autopsy case and the first unoperated case of the mucoepidermal carcinoma of the esophagus in the literature.

CASE HISTORY

A 53-year old Japanese female was admitted to the hospital on 27 September 1976. She had a two-month history of dysphagia and marked weight loss. On admission, she showed severe emaciation and dehydration. All laboratory data were within normal limits. Esophageal roentgenograms and fiberscopy were performed the day following admission and a constricting lesion was found in the esophagus, 26 cm. from the incisor teeth. At the same time, biopsy was done and a diagnosis of squamous cell carcinoma was made. Preoperative irradiation (total 4,000 rads) was performed and the tumor was significantly decreased in size. But she had not obtained sufficient recovery of a nutritional state, so that the radical operation was not performed.

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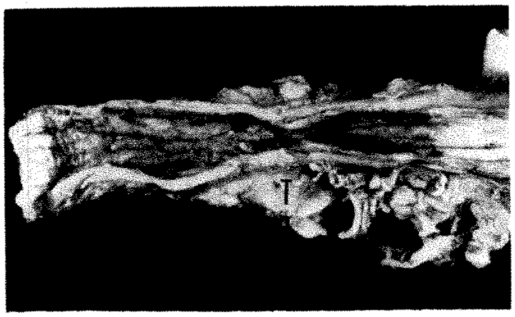

Fig. 1—Gross photograph of the esophageal primary tumor. Annular and indurated tumor (T) narrowed the esophageal lumen.

Approximately one month after hospitalization, she developed acute bronchopneumonia with abscess formation and then pursued a downhill course. The patient finally expired on 1 November 1976. The duration from the onset of dysphagia to death was 3.5 months. An autopsy was performed.

Pathological Findings

Gross features of the esophageal tumor:—The main esophageal tumor was located 8 cm. above the esophagogastric junction and measured 4 cm. in length. The tumor was annular, indurated and the mucosal surface was ulcerated. The esophageal lumen at the tumor was extremely narrowed (Fig. 1). Section through the tumor showed thickened and fibrotic esophageal wall.

Light microscopic features of the esophageal tumor:—Routinely processed sections showed the tumor to be composed of many nests of relatively uniform focally keratinizing squamous epithelial cells admixed with frequent glandular or sometimes cystic structures lined by flattened or cuboidal epithelial cells (Figs. 2 and 3). These glandular elements of the tumor contained Alcian blue and mucicarmine positive mucin. The neoplastic cells invaded muscle layer and focally reached the adventitia. The tumor cells also infiltrated among the smooth muscle fibers along the muscle layer for approximately 4 cm. in length.

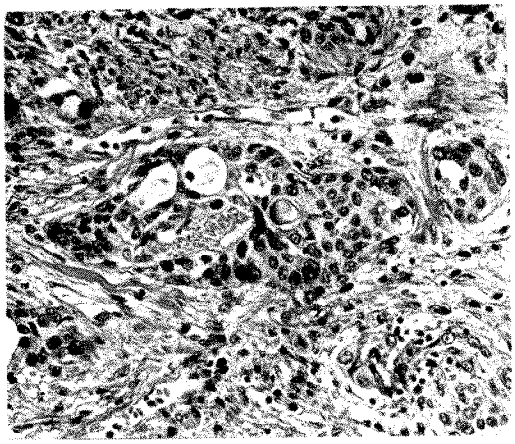

Fig. 2—Light microscopically, the primary tumor resembled mucoepidermoid carcinoma of the salivary gland characterized by mixture of focally cystic glands and keratinizing squamous cells (Hematoxylin and eosin, original magnification x300).

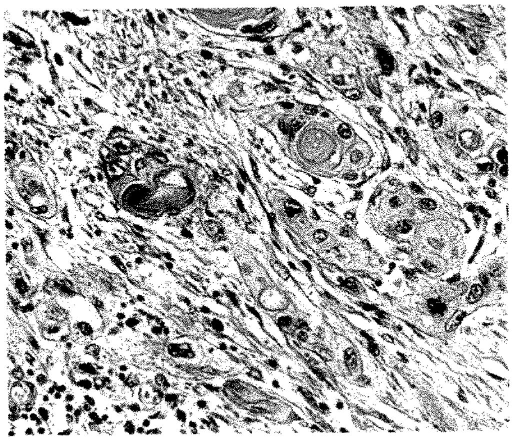

Fig. 3—The primary tumor occasionally showed predominant squamous pattern with many squamous pearls (Hematoxylin and eosin, original magnification x300).

Other autopsy findings:—Direct extension of the tumor, which formed a 2 cm. cystic cavity, was noted between the esophagus and trachea. No other metastatic lesion was identified. Other pertinent findings in-

TABLE I

REVIEW OF THE LITERATURE ON MUCOEPIDERMOID CARCINOMA OF THE ESOPHAGUS

Cases	Age	Sex	Location	Metastasis	Outcome
1[2]	54	F	lower third		14 years survived
2[2]	47	M	at the junction of the upper and middle thirds	widespread (clinically)	1 year died
3[4]	47	M	lower third	recurrent tumor extended into the pericardium, heart, and thoracic aorta.	40 months died*
4[4]	66	M	lower third	liver, mediastinal and gastric lymph nodes (at the time of operation)	6 months died
5[6]	67	M	lower third	periesophageal lymph nodes (at the time of operation) no residual tumor or metastasis (postmortem examination)	2nd postoperative day, died*
6[5]	63	F	just above the thoracic inlet	widespread (clinically)	17 months died
7[3]	57	M	esophagogastric junction	aortic arch and retroperitoneal lymph nodes (at the time of operation)	3.5 months died

*Postmortem examination.

cluded radiation pneumonitis and bronchopneumonia of both lungs accompanied by right pyothorax, which were considered to be the immediate cause of death.

COMMENT

Unlike the adenosquamous cell carcinoma occurring at the esophagogastric junction, our present tumor showed histological similarity to the mucoepidermoid carcinoma of the salivary gland. Its main submucosal location supported the previously suggested origin of this tumor as being from the esophageal glands.[2]

The results of our review of previously reported cases of mucoepidermoid carcinoma of the esophagus are summarized in Table I. As in our case, the tumor has occurred in elderly persons, 47 being the youngest. Most of the tumors were found in the lower part of the esophagus. Although it has been previously suggested that this tumor should offer better prognosis than ordinary squamous cell carcinoma, our review showed the invasive and metastatic nature of this tumor. Further accumulation of data on similar tumors seems to be required until its exact behavior and proper treatment can be predicted.

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Clinical Vignette

Improvement in Esophageal Abnormalities in a Patient with Scleroderma and Features of Polymyositis

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A patient with clinical features of both scleroderma and polymyositis, including esophageal dysfunction typical of scleroderma is described. Regression of her illness occurred along with manometric improvement in the esophageal dysfunction. Improvement in esophageal abnormalities in scleroderma has not been previously reported.

Motor abnormalities of the esophagus and lower esophageal sphincter (L.E.S.) are common in many of the connective tissue diseases, especially in scleroderma where their incidence approaches 80%, if manometry is employed in their detection.[1] In scleroderma there is generally progressive deterioration in symptoms. Occasionally, however, spontaneous regression of the skin manifestations has been observed but this does not correlate with improvement in esophageal motor function.[2] Indeed, although the esophageal dysfunction may remain static for years, its improvement or resolution has not been reported previously.

In contrast to scleroderma in which the distal (smooth muscle) portion of the esophagus is affected, motor abnormalities in polymyositis are due to weakness of the pharyngeal muscle and the striated muscle of the upper third of the esophagus. This is manifested manometrically by absent or diminished swallowing responses in the pharynx, upper esophageal sphincter and proximal esophagus.[3] "Overlap" syndromes having clinical and manometric features of both scleroderma and polymyositis have also been described.

The following report describes a patient with scleroderma and Raynaud's phenomenon with some features of polymyositis who demonstrated manometric improvement in esophageal aperistalsis and return of L.E.S. tone along with remission of some of the clinical manifestations of her disease.

CASE REPORT

D. C., an 18-year old Caucasian woman first presented in 1968 with symptoms of exertional dyspnea, bilateral Raynaud's phenomenon of her hands, regurgitation

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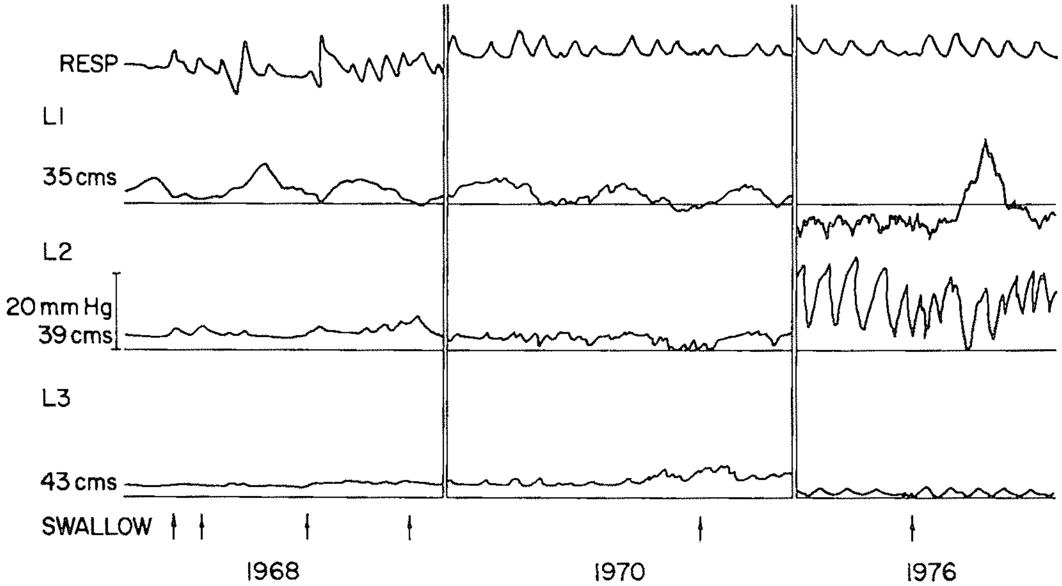

Fig. 1—*Esophageal manometry:*—Uppermost tracing records respirations (RESP). L1, L2 and L3 are recordings made from radially oriented orifices located 4 cm. from each other. The horizontal line on each tracing indicates atmospheric pressure. All distances are in centimeters from the incisors. The numbers at the bottom of each column represent the year the tracing was made. L1 is in the body of the esophagus, L2, in the L.E.S. and L3 in the gastric fundus. *Left* (1968), contractions are of low amplitude. No L.E.S. is detectable. *Middle* (1970), Contractions are still of low amplitude and some occur spontaneously (L1). No L.E.S. is detectable. *Right* (1976), the amplitude of contractions had increased. An L.E.S. is now identifiable and relaxes on swallowing.

and heartburn of about one year's duration. On physical examination, the only abnormalities noted were symmetrical swelling of the metacarpophalangeal and proximal interphalangeal joints of both hands, tapering of the digits and bound-down, tight skin over her hands and shins. The *L.E.* cell preparation and rheumatoid factor were negative, a chest x-ray and barium swallow with a ciné of the esophagus were interpreted as being normal. Esophageal manometry and pH reflux testing were performed by previously described technics.[4] The presence of gastroesophageal reflux was documented by intraesophageal pH recording. Esophageal manometry recorded from radially-oriented catheter orifices, failed to detect a lower esophageal sphincter (Fig. 1). In the body of the esophagus, swallowing complexes were mostly peristaltic but of low amplitude and simultaneous contractions of similar amplitude frequently followed swallows (Fig. 2). No spontaneously occurring nonperistaltic waves were present. In the upper third of the esophagus, low amplitude peristaltic waves and a low resting upper esophageal sphincter (U.E.S.) pressure (10 mm. Hg.) were recorded (Fig. 3).

On the basis of these findings, a diagnosis of scleroderma was made and treatment initiated with prednisone and para-aminobenzoic acid. In addition, she was instructed in an antireflux regimen of elevation of the head of the bed and hourly antacids.

Her symptoms improved and the medications were discontinued one year later. A barium swallow at this time, however, demonstrated a slightly dilated esophagus without peristaltic activity, and a small

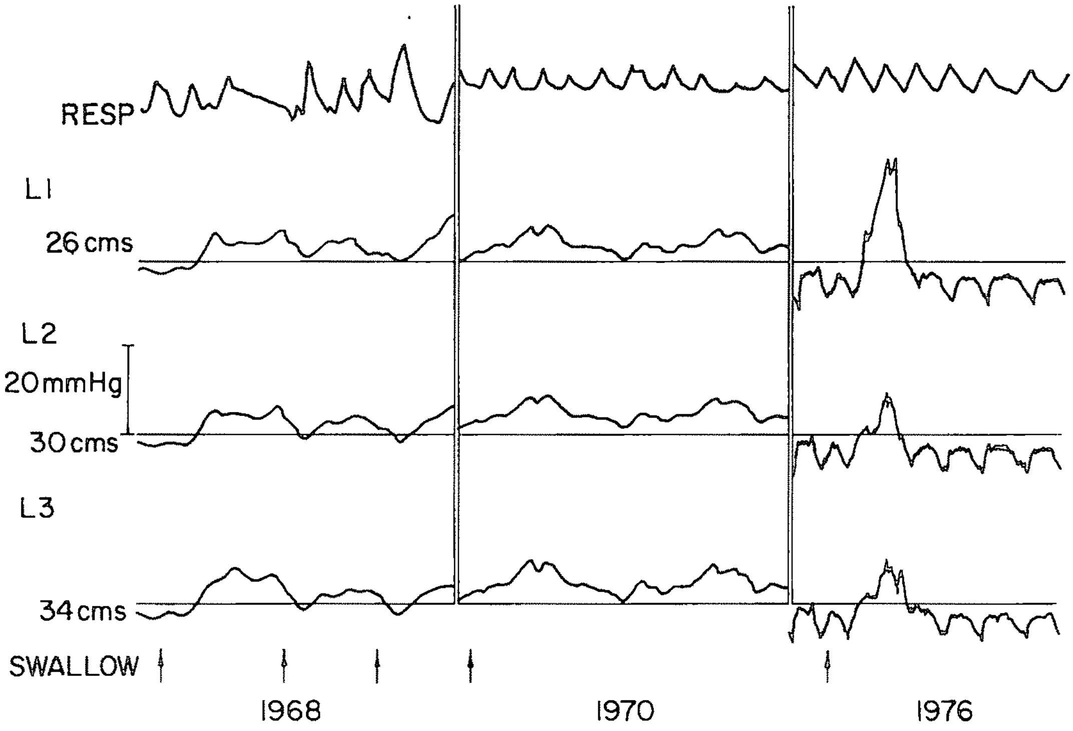

Fig. 2—*Esophageal manometry:*—All three leads are in the body of the esophagus. *Left* (1968), Swallows result in low amplitude simultaneous contractions. *Middle* (1970), swallows still result in nonperistaltic contractions. Spontaneous nonperistaltic contractions are also present. *Right* (1976), amplitude of contractions has markedly increased and they are now occasionally peristaltic.

hiatal hernia. These findings were again confirmed on endoscopy which also revealed the presence of erythema and friability in the hernial sac but a normal appearing esophageal mucosa. An esophageal biopsy was normal. The *L.E.* cell preparation remained negative. The chest x-ray was unchanged but pulmonary function studies demonstrated a mild restrictive defect. Treatment with antacids was continued.

In January of 1970, she was again hospitalized because of progressive muscular weakness. She continued to complain of heartburn and in addition, was experiencing dyspareunia. On physical examination, the skin changes noted previously were unchanged. There was proximal muscle weakness predominantly affecting the upper extremities. A pelvic examination demonstrated a dry and atrophic vaginal mucosa. The serum aldolase was normal, but the creatine phosphokinase (C.P.K.) was consistently elevated at one and a half to two times normal. An electromyogram revealed a myopathic pattern in the proximal muscles. A biopsy of the involved triceps muscle was normal. A diagnosis of polymyositis was made and treatment initiated with high-dose prednisone. At this time, the barium examination of the esophagus was unchanged but the small bowel follow-through showed slight generalized dilatation and slow transit of barium distally, compatible with sclerodermatous involvement of the small bowel. On treatment in the hospital, the patient showed subjective but not objective improvement in muscle strength. The prednisone was decreased to

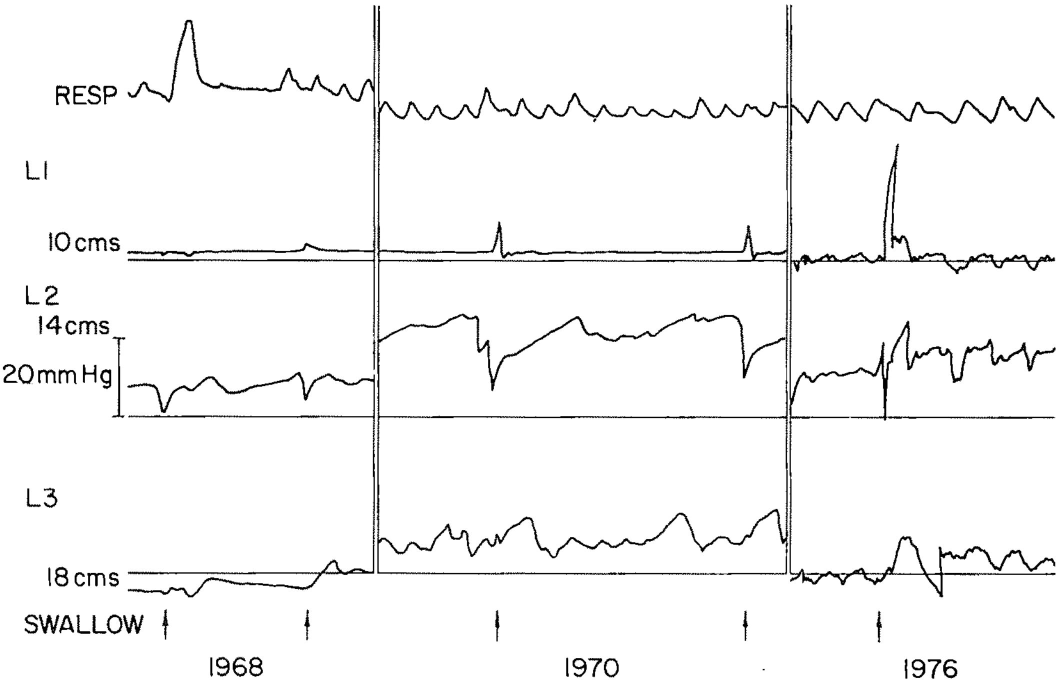

Fig. 3—*Esophageal manometry:*—L1 is in the pharynx, L2 in the U.E.S. and L3 in the upper esophagus. *Left* (1968), low pressures recorded at all three sites but the progression from pharyngeal pressure change to relaxation of U.E.S. is normal. *Middle* (1970), pharyngeal and U.E.S. pressure have increased but the amplitude of contractions in the upper esophagus remains low. *Right* (1976), pharyngeal pressures are higher, otherwise essentially unchanged from 1970.

maintenance doses and weekly Methotrexate was added.

• Seven months later she was again hospitalized because of increasing dysphagia for solids and also because of retrosternal pain precipitated by hot and cold liquids. Physical examination was unchanged. Antinuclear factor (A.N.F.) was negative. Aldolase and C.P.K. were normal. Esophageal manometry showed absence of peristalsis in the distal two-thirds of the esophagus with no detectable L.E.S. (Figs. 1 and 2). Swallows either did not elicit a response, or were followed by simultaneous contractions of low amplitude. Spontaneously occurring simultaneous contractions of low amplitude were also frequent. Peristalsis in the upper third of the esophagus was normal and had increased in amplitude as had the resting U.E.S. pressure (Fig. 3). Endoscopy revealed an erythematous and friable mucosa with superficial ulcerations in the distal third of the esophagus and a narrowing at 39 cm. This was treated by dilatation with Eder-Puestow dilators from 35-45 French and a continuous intraesophageal antacid drip.[5, 6] The dysphagia resolved and the muscle weakness improved. She was discharged on weekly Methotrexate without prednisone. In addition, she was to continue the intraesophageal antacid drip as an out-patient during the night. The Methotrexate was discontinued after one year.

Apparently unrelated to these other problems, the patient developed temporal lobe epilepsy in 1971 and was treated with phenobarbital, diphenylhydantoin and later also mysoline with control of her seizures.

Between July 1971 and September, 1975 she had two endoscopies for recurrent heartburn and dysphagia associated with ulcerative esophagitis, each time following discontinuation of the antacid drip for several weeks. Endoscopically and radiologically the stricture did not recur. Sclerodermatous skin changes became prominent over her forehead, fingers, shins and mouth and resulted in some inability to open her mouth widely. Fingertip ulcerations and telangiectasia of the skin of the chest became evident in 1972.

The A.N.F. became positive to a titer of 1/20 in 1973 but the C.P.K. and aldolase remained normal. Three-day fecal fats were mildly elevated at 19.3 mEq./day (normal: less than 15 mEq./day) in April, 1975.

She continued to have only occasional heartburn and dysphagia but was readmitted for investigation in August, 1976 when there was an apparent improvement in certain features of her illness. On examination there was telangiectasia over the chest and face. The skin was bound down and thickened, primarily in the forearms and legs but there was now only minimal involvement of the hands. Only minimal sclerodactyly was present in comparison to a year before. Muscle strength in the proximal extremities and neck was slightly decreased but the E.M.G. had returned to normal. Pulmonary function studies were now normal. A pelvic examination showed marked improvement in the condition of the vaginal mucosa, coincident with disappearance of the dyspareunia. A ciné esophagogram now demonstrated definite peristalsis. The hiatal hernia was still present and reflux of barium was again demonstrated. On endoscopy, there was now evidence of peristalsis and tertiary contractions in the distal half of the esophagus but no mucosal ulceration or stricture formation. The A.N.F. was positive in a titer of 1/10 but negative at higher dilutions. The latex-fixation test for rheumatoid factor was negative. A Schirmer test for lacrimation was normal. Fecal fat excretion had increased to 30.5 mEq./day.

The most striking changes were noted on esophageal manometry. An L.E.S. was clearly identifiable with a gastrosphincteric gradient[7] of 11 mm. Hg. and with normal relaxation occurring on deglutition (Fig. 1). In addition, normal peristaltic activity was now present in the distal esophagus (Fig. 2). Simultaneous contractions were still seen but were of higher amplitude than previously. The upper esophagus demonstrated normal peristalsis and a normal U.E.S. pressure (Fig. 3). Mecholyl 7.5 mg. subcutaneously produced no change in baseline pressure.

COMMENT

This patient presented with clinical features and manometric findings (Figs. 1, 2 and 3) compatible with a diagnosis of scleroderma and later developed features of polymyositis. Esophageal manometry initially showed low amplitude peristaltic waves with no detectable L.E.S. and frequent low amplitude simultaneous contractions following deglutition in the distal two-thirds of the esophagus. The upper third of the esophagus demonstrated the presence of peristaltic activity but it was of low amplitude and associated with a low U.E.S. pressure.

Two years later, when the patient first complained of dysphagia, the dysfunction of the distal esophagus progressed to aperistalsis (Figs. 1, 2 and 3) and only low amplitude simultaneous contractions were seen in response to swallows. Low amplitude spontaneous (tertiary) contractions were frequently noted. The amplitude of peristalsis in the upper esophagus and the resting U.E.S. pressures had returned to normal. These changes were associated with ulcerative esophagitis on endoscopy. Esophageal stricture then developed and the patient required esophageal bougienage for symptomatic relief. Eight years after her initial presentation and after six years of intermittent therapy with a nocturnal intraesophageal antacid drip, however, a marked improvement was present on esophageal manometry. Peristaltic activity had returned to the lower esophagus and a recognizable L.E.S. was now present (Figs. 1, 2 and 3). These findings correlated with the absence of esophagitis at endoscopy but the patient was still symptomatic of dysphagia and heartburn. At the same time, improvement in the cutaneous manifestations of the disease, and resolution of the restrictive pulmonary dysfunction had occurred.

This patient had an "overlap" syndrome with features of both scleroderma and polymyositis but with esophageal involvement resembling that seen in scleroderma.[8-10] Improvement in the esophageal abnormalities, similar to the improvement elsewhere, was most likely spontaneous, although this has not been previously reported. The role which the various drugs she received had to play in this improvement is not clinically evident, as none have been proven of value in patients with scleroderma. On the other hand, the effect of prolonged intraesophageal antacid drips in patients with esophageal dysfunction due to scleroderma has not been evaluated and allows one to speculate on the role this form of therapy had to play in the improvement seen in this patient.

With reflux of gastric contents, a vicious cycle is set up in which esophagitis leads to impaired acid clearing[11] and, at least in cats, to decreased L.E.S. tone and responsiveness to pharmacological stimuli.[12, 13] In scleroderma it has been found that only minimal abnormalities are often detectable on light microscopy in areas of marked manometric abnormality.[14] It is therefore possible that some of the abnormalities, at least early in the disease, are due to abnormal function rather than to changes in structure and therefore may be reversible. This is supported by evidence of abnormal responsiveness of the L.E.S. to direct muscle stimulants and to direct and indirect cholinergic stimuli in various stages of scleroderma.[15] Early aggressive antireflux therapy may therefore modify the progression of the esophageal disease in scleroderma.

Reflux esophagitis, with its complications, significantly contributes to the morbidity of this condition and is one of the few abnormalities in scleroderma that is amenable to symptomatic therapy. Antireflux therapy including a continuous intraesophageal antacid drip, may play a role in preventing the progression of the esophageal dysfunction by interrupting the cycle of: reflux → esophagitis → impaired acid clearing and decreased L.E.S. pressure → more esophagitis.

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Clinical Vignette

Systemic Mercury Intoxication Following Rupture of a Miller-Abbott Tube

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Following rupture of a Miller-Abbott tube mercury bag a 39-year old woman, postoperative for resection of the right colon for diverticulosis and diverticulitis, developed signs and symptoms of systemic mercury intoxication. A small bowel fistula allowed the metallic mercury to aggregate in retroperitoneal tissues setting up an environment which was conducive to conversion of metallic mercury to divalent mercury, an absorbable product. Analysis of brain, kidney and urine following her demise showed markedly elevated mercury levels. To our knowledge this is the only reported case of such a complication. Clinicians should be wary of elemental mercury in the gastrointestinal tract in patients with suspected or proven enteric fistulas.

The use of a mercury weighted tube is standard treatment for decompression of small bowel obstruction. The present case illustrates systemic mercury intoxication, characterized by central nervous system signs and an enterocolitis, following the rupture of a Miller-Abbott tube mercury bag. The diagnosis was confirmed by elevated urinary, brain and kidney mercury concentrations.

CASE REPORT

A 39-year old female was admitted to Larson AFB Hospital, Washington, 18 February 1963 with the chief complaint of intermittent right lower quadrant abdominal pain of five years duration, associated with passage of bright red blood and mucus in the stools. A previous barium enema had demonstrated right-sided diverticulosis.

Physical examination revealed right lower quadrant tenderness and a liver edge palpable 2 cm. below the costal margin. The examination, otherwise, was within normal limits.

The day following admission the patient was taken to surgery for a right hemicolectomy and an end-to-end iliocolic anastomosis, as treatment for diverticulosis and diverticulitis of the right colon. The resected colon specimen showed diverticulosis and diverticulitis when examined by the pathologist.

Initially, the patient's course was unremarkable, except for a low-grade intermittent fever. On the 10th postoperative day the patient developed abdominal distention with x-ray findings consistent with small bowel obstruction. A Miller-Abbott tube was passed and placed on suction. The mercury-filled bag ruptured spontaneously three days later and was replaced by a second similar tube. The abdominal disten-

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TABLE I

MERCURY LEVELS

Source	Patient level	Normal level
Brain	0.56 ppm.	0.10 ppm.[6]
Kidney	21.3 ppm.	2.75 ppm.[6]
Urine	242 mcg./l.	< 50 mcg./l.[4]

tion persisted, despite the Miller-Abbott tube, with the development of right flank tenderness. The patient was taken to surgery on the 14th postoperative day for incision and drainage of an abscess in the right flank. Over the next 10 days, green stool drained through the incision in the right flank. Pseudomonas was cultured from the drainage; chloramphenicol and tetracycline were started. On the 24th postoperative day an ileocolostomy was performed. By the 34th day the drainage was considerably reduced, and an operative closure of the ileocolocutaneous fistula was planned. Over the next 24 hours, the patient began pouring copious amounts of fluid through both the ileocolocutaneous fistula and the rectum. On the 36th day the patient developed a mild tremor with considerable weakness and tonic-flexed posturing of the upper extremities. On the following day the patient developed hyperpnea with a gross tremor and purposeless rotating movements of the eyes. The patient expired on the evening of the 37th day.

Necropsy findings of the abdomen demonstrated a cutaneous fistula, extending from the right lateral abdominal wall into the retroperitoneal space behind the right kidney and the right lateral gutter. Multiple globules of metallic mercury, measuring approximately 3 cc., were present in the retroperitoneal cavity. The pathologic findings of the small and large bowel were that of an acute enterocolitis. In addition a fistula extended from the distal ileum to the right retroperitoneal area.

Toxicology studies were performed on postmortem urine and tissue from the kidney and brain. The results are shown in Table I. Mercury determinations were done at the Sixth United States Army Medical Laboratory. Personal communication with the chemist indicated he did not know the exact name of the analytical procedure but the general method was as follows: Organic digestion with nitric and sulfuric acid, extraction with chloroform, color development with dithiazone. Test results were then read in a spectrophotometer.

COMMENT

Systemic mercury toxicity, as a complication of rupture of a mercury-filled intestinal decompression tube, has not been previously reported. Fistulas and granuloma formation have been reported as the most common complication following rupture of a mercury-filled tube within the lumen of the intestine.[1, 2] Recently, the direct observation by sigmoidoscopy of metallic mercury within a fistula tract was described.[3] Blood mercury levels were above normal, however, the patient exhibited no signs of systemic mercury toxicity.

Systemic absorption of mercury did occur as shown by the abnormal urine and tissue levels in Table I. The urinary level of 242 mcg. Hg./l. is an "above normal" level. Jacobs, et al, found that 20% of urine from nonmercury exposed individuals contained mercury, but rarely above 50 mcg. Hg./l.[4] The range of 100 to 300 mcg. Hg./l. is suggestive of excessive exposure to mercury.[5] Monitoring urinary levels of mercury is the commonest method for determining exposure, however, the level is not specific for the occurrence of systemic symptoms. The tissue levels in the kidney

(21.3 ppm. Hg.) and in the brain (0.56 ppm. Hg.) are well above the levels of 2.75 ppm. Hg. and 0.10 ppm. Hg., respectively, established in autopsied, nonmercury exposed human tissue.[6]

To effect systemic absorption of mercury, the conversion of metallic mercury to divalent mercury (Mercuric ion) is necessary.

$$Hg^{o} \rightarrow Hg^{+2} +^{2e-}$$

In absence of a break in the integrity of the intestinal mucosa, free metallic mercury normally passes through the gut rapidly enough to preclude significant conversion to divalent mercury. With a site, however, for mercury stasis, i.e. a mercury-contained fistula and the presence of water and chloride ion at body temperature, an oxidative-reduction reaction slowly occurs with the transformation of metallic mercury to divalent mercury.[7]

Two clinical manifestations of systemic mercury toxicity were exhibited (tremor and enterocolitis) in this patient. The tremor in mercury poisoning is classical and itself implies toxicity of the central nervous system. The tremor is fine, rhythmical, static; interrupted by sudden coarse, jerky movements and aggravated by voluntary movements. An enterocolitis, characterized by diarrhea, tenesmus, ulceration and hemorrhage, has been described, appearing up to several weeks after ingestion of inorganic mercury compounds.[8]

Systemic mercury toxicity following rupture of a mercury-contained intestinal decompression tube is a previously unrecognized complication. The association of mercury bag rupture with a break in the intestinal mucosa should alert the clinician to the possible occurrence of systemic toxicity. If clinical signs of mercury toxicity are evident such patients should be tested by urine mercury levels to ascertain the diagnosis.

ACKNOWLEDGMENT

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Clinical Vignette

Calcified Mucinous Adenocarcinoma of the Stomach

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Two cases of unusual mucinous adenocarcinomas of the stomach with calcification are reported. One of the cases demonstrated hypercalcemia. Endoscopic verification of the calcifications was confirmed. This report represents the 49th and 50th reported cases in the world's literature.

The occurrence of calcification in gastric cancer is extremely rare. There are 48 cases in the published literature since the first case report by Gruber in 1913.[1] The purpose of this paper is to report two additional cases of this rare entity with endoscopic observations.

CASE REPORTS

Case 1:—A 22-year old female entered the hospital because of pallor, weight loss, epigastric pain, abdominal distention and dysphagia of seven months' duration. On examination, she appeared pale and an abdominal fluid wave was demonstrated. A hard, epigastric mass was felt.

The serum calcium was 14 mg.% (normal values: 9-11 mg.%); the ionizable calcium was 6.5 mg.% (normal 4.2-5.2 mg.%) and inorganic phosphorus was 4.1 mg.% (normal: 2-4 mg.%). The hematocrit was 36% and the hemoglobin was 10.8 gm.%. A paracentesis was performed and cytologic examination of the ascitic fluid demonstrated Class V cells. Survey film of the abdomen showed multiple tiny punctate calcifications in the left upper abdominal quadrant (Fig. 1). A gastrointestinal series demonstrated an infiltrating and rigid mass in the stomach, extending from the esophagogastric junction to the antrum, with thickening of the gastric wall, loss of normal mucosal pattern and luminal protrusion. Many tiny punctate calcifications outline the mass (Fig. 2). Esophagogastroscopy was performed demonstrating a large ulcerated mass occupying most of the visualized stomach to the pylorus. The gastric mucosa bled easily and superficial chalky-white plaque could be identified throughout the tumor mass (Fig. 3).

The patient declined surgery and expired 15 days after admission. At autopsy, a large, gelatinous mass with evident tiny punctate calcific placques occupied most of the stomach. The tumor extended downward to include the initial portion of the duodenum and upward to include part of the cardiac end of the esophagus. There were metastases to the abdominal lymph

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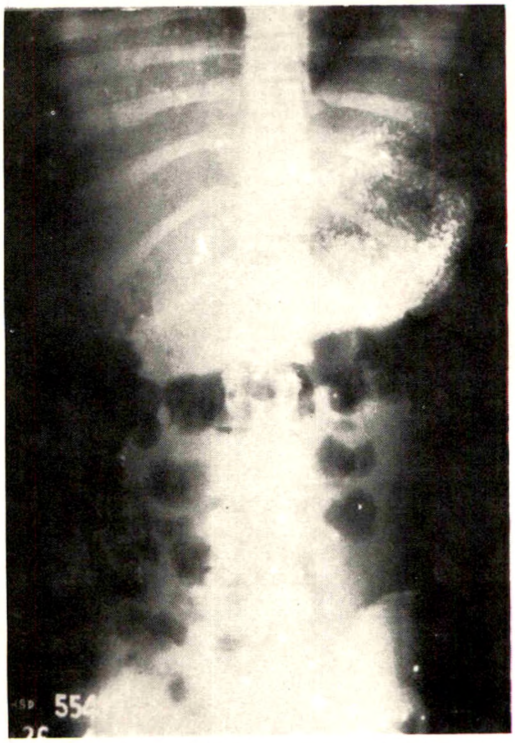

Fig. 1—Case 1, multiple punctate calcifications in the left upper abdominal quadrant.

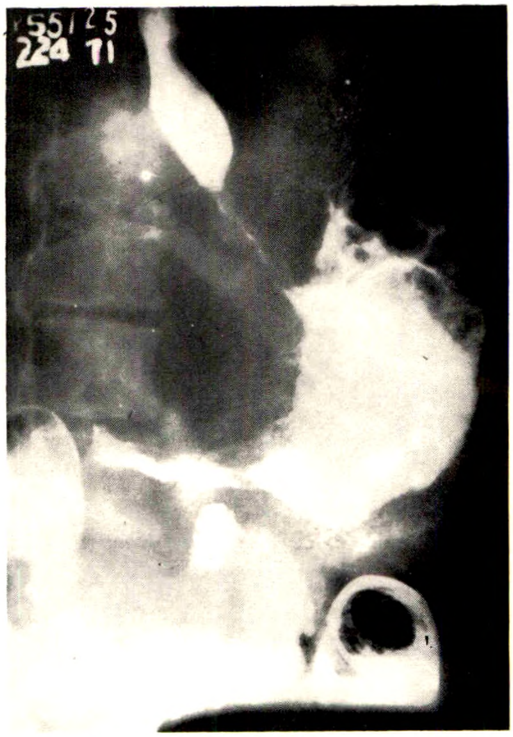

Fig. 2—Case 1, punctate calcifications outline an infiltrating and rigid mass in the stomach.

nodes, peritoneum, liver, spleen, ovary, small and large intestines. Histologic examination demonstrated a mucus-secreting adenocarcinoma (Fig. 4). The extensive foci of calcification corresponded to the areas of cellular mucin secretion.

Case 2:—A 43-year old woman was admitted to the hospital because of a three-month history of early satiety and weight loss. One month prior to admission, an episode of hematemesis had occurred. On examination, she appeared emaciated, however, no other pertinent physicial findings could be elicited. The hemoglobin was 10.5 gm.%; the hematocrit was 34%. The alkaline phosphatase was 5.6 Bodanski units. The serum calcium was 9.0 mg.% and the inorganic phosphorus 4.3 mg.%. Cytologic examination of the ascitic fluid was Class IV. A survey film of the abdomen demonstrated innumerable micronodular calcifications in the left upper quadrant. A gastrointestinal series demonstrated a large infiltrating tumor in the antrum extending to the lesser curvature of the stomach. Endoscopic and microscopic findings were similar to those described in Case 1.

The patient refused any type of treatment and was, therefore, discharged from the hospital. She was lost to follow-up.

COMMENT

The demonstration of calcium deposits within an adenocarcinoma of the stomach is extremely rare when compared to the incidence of the majority of malignant gastric neoplasms. Although the first case was described by Gruber in 1913,[1] the first case in American literature was not described until 1954.[2] A total of 48 cases of this variant neoplasm has been reported

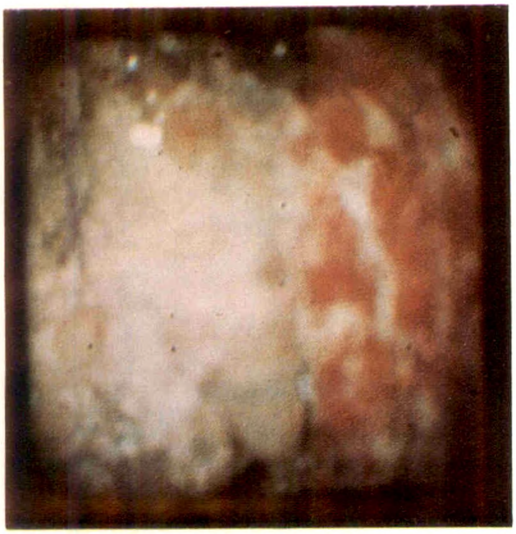

Fig. 3—Case 1, chalky-white plaque in the tumor mass.

prior to our two cases. All of these tumors have been mucinous adenocarcinomas.

Both our patients were young (22 and 43 years). The occurrence of this unusual carcinoma in a younger age group has been noted by D'Altorio.[3] According to McAfee and Donner,[4] one should consider, in the differential diagnosis of left upper quadrant calcification: 1. pancreatitis, 2. old granulomatous disease of the spleen, 3. lesions of the left kidney and adrenal gland, 4. retained opaque material in the stomach, 5. hyperparathyroidism, 6. Vitamin D intoxication, 7. chemical necrosis of the gastric mucosa, 8. benign stomach tumors and 9. leiomyomas and hemangiomas. It is of interest that our first patient had hypercalcemia on one occasion. Most of these mucinous adenocarcinomas show a uniform distribution of calcification throughout the tumor as is seen in tumors of the ovary, thyroid and breast, and meninges.

According to Myo Lwin,[5] the essential radiological findings of pathologically proven cases of calcified mucinous adenocarcinoma are the presence of mottled, stippled, granular, punctate and miliary calcifications in an infiltrative lesion of gastric mucosa. In the present report, the first case showed a punctate pattern of calcification although Case 2 presented a miliary aspect. In both cases, the calcification corresponded to the anatomic topography of the stomach in the abdominal cavity. Similar to other reported cases, it was the simple survey film of the abdomen and not the gastroduodenal barium x-rays which were the most distinctive features of the diagnosis of this rare gastric tumor.

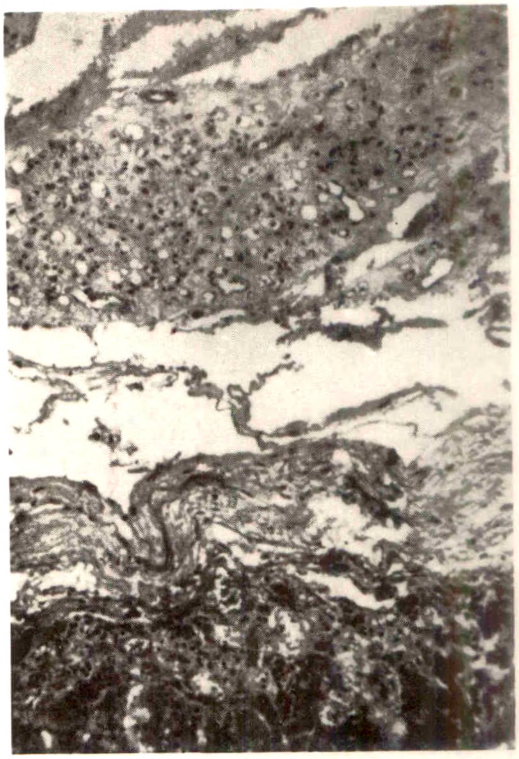

Fig. 4—Case 1, the lower part of the field showing numerous anaplastic cells with typical seal ring and mucin areas. (Hematoxylin and eosin stain, original magnification x150).

Reports on endoscopic findings are scanty[6, 7] and we present photographic documentation of these rare tumors for the first time, to our knowledge.

The process by which pathologic calcification in this mucinous adenocarcinoma is not known but several theories have been proposed: 1. an abnormally high concentration of calcium and phosphate in the serum with subsequent precipitation of calcium phosphate salts in the normal tissue, or 2. calcium precipitation occurring in degenerative necrotic tissue with normal levels of serum calcium. Previous reports[8-12] have emphasized the decrease in cellular metabolism secondary to necrotic and ischemic function of the areas of the stomach resulting in relative alkalinity and subsequent calcification, since calcium salts, especially phosphates and carbonates, are soluble in acid solution but are hardly soluble in alkaline solution.

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Clinical Vignette

Retroperitoneal Lymphangioma

A Case Report with Review of the Literature

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A case of retroperitoneal cystic lymphangioma is reported. Added to the 42 cases of retroperitoneal lymphangioma found from the English literature, this brings up the total of cases reported to date to 43.

A critical review of the clinical picture and management of this condition is presented on the basis of these reported cases.

Lymphangiomas are tumors composed of lymphatic spaces and vascular elements. About one-third of all lymphangiomas occur in the neck[1] and are also known as cystic hygromas. Uncommon sites for the tumor include the groin,[2] bone,[3] mediastinum,[4] uterus,[5] stomach,[6] small intestine,[6] colon,[7] rectum,[7] omentum,[4] mesentery,[4] spleen,[8] liver,[3] and retroperitoneal space.[9] Rauch[9] collected 20 cases of retroperitoneal lymphangiomas from the literature and added two of his own. We have found 20 additional ones since then, making a total of 42 cases of retroperitoneal lymphangioma in the English literature to date. The rarity of the lesion has prompted this case report and review of the literature.

Case Report

A 13-year old boy was hospitalized on 26 August 1974 with the complaints of distention of the abdomen of three months' duration. It was insidious in onset and gradually progressive. He had a fall 20 days prior to admission after which he had moderately severe, poorly localized pain in the abdomen radiating to the back for two days. He also had five to six

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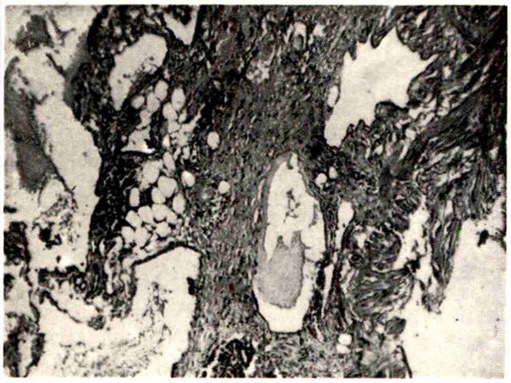

Fig. 1—Section through the cyst wall showing multiple vascular channels interspersed with adipose tissue and lymphoid aggregates. Thick bundles of smooth muscle are seen near the cyst lining (Hematoxylin and eosin, original magnification x30).

vomitings, which were green in color. The patient was otherwise asymptomatic.

Physical examination revealed a well nourished youth with distended abdomen. On palpation a large lobulated swelling was felt, occupying the epigastric, left hypochondrial and umbilical regions. The swelling was immobile with ill-defined borders and presented cross fluctuation. Areas of varying resonance were present over the swelling. There were no other masses. The flanks were resonant.

Laboratory studies disclosed a hemoglobin of 13.8 gm./100 ml.; white blood cell count of 7,500/cu. mm. and erythrocyte sedimentation rate of 30 mm. for the first hour. The urine showed traces of albumin. Blood sugar and urea were normal. The serum total protein was 5.1 gm./100 ml. with an albumin of 2.7 gm./100 ml. Alkaline phosphatase was 6.5 K.A. units. The serum bilirubin and transaminases were normal.

Laparotomy was performed on 11 September 1974 and showed a multiloculated retroperitoneal cystic swelling extending into the lesser sac, mesentery and transverse mesocolon. One liter of blood-stained fluid was removed from a large cyst. The cysts in the right and left hypochondria were decompressed. The cavity was drained by a tube which was retained for one week. The patient became asymptomatic and no recurrence was noted after one year.

The surgical specimen consisted of a multilocular cyst measuring 7 × 5 ×2 cm. The cyst wall was spongy in consistency and the inner lining was smooth. The section of the cyst wall showed that it was composed of a loose connective tissue containing thick bundles of smooth muscle near the inner surface and having an interrupted endothelial lining (Fig. 1). In addition, a large number of lymphatic and blood vascular channels were seen within the cyst wall interspersed with aggregates of lymphoid tissue. Histopathologically it was reported as a lymphangioma.

COMMENT

Harrow,[10] in an extensive review, estimated that over 600 cases of mesenteric cysts had been reported until 1957 but found only 70 instances of retroperitoneal cysts, of which 14 were lymphatic. Rauch[9] summarized the features of 22 cases of retroperitoneal lymphangiomas, including two of his own. Table I summarizes the case reports of 21 additional lymphangiomas of the retroperitoneal region including the one reported in the present communication.

According to Rosanger,[11] the following criteria should be fulfilled for the diagnosis of lymphangioma.

1. A cyst with or without an endothelial lining but not having a cuboidal or columnar epithelium.

2. Small lymph spaces in the wall of the cyst.

TABLE I

Clinical Data of 21 Patients with Retroperitoneal Lymphangioma

S. no.	Author	Year	Age (yr.)	Sex	Duration of symptoms	Symptomatology	Location of tumor	Cyst fluid	Unilocular or multilocular	Treatment	Survival (A = alive; W = well)	Diagnosis
1	Norflett, et al[13]	1959	9	M	2 days	Abd. pain Fever	Rt. lumbar	Serous	Multilocular	Excision	A & W 1 mo.	Cystic lymphangioma
2	Raszowski, et al[14]	1959	37	F	6 mo.	Operated 7 yr. ago for mass Pain abd.	Rt. ileac fossa	Serous	Multilocular	Excision	A & W 4 mo.	Cystic lymphangioma
3	Barret, et al[15]	1960	41	M	4 days	Abd. pain vomiting	Lt. lumbar	Serous	Unilocular	Excision	A & W 23 mo.	Cystic lymphangioma
4	Larson, et al[4]	1961	3/12	M	3 mon.	Abd. mass	Rt. abdomen	?	?	?	?	Lymphangioma
5	-do-		2	F	2 yr.	Abd. mass	Rt. ileac fossa	?	?	?	?	Lymphangioma
6	Schlicht, et al[16]	1962	12	M	1 yr.	Abd. pain	Rt. abdomen	Serous	Unilocular	Excision	Survived operation. No follow-up.	Cystic lymphangioma
7	Thrupp[17]	1963	16	M	2 days	Abd. pain suggestive of appendicitis	Root of mesentery	Turbid yellowish	Multilocular	Excision	A & W 5 mo.	Cystic lymphangioma
8	Gordon, et al[18]	1964	37	F	3 yr.	Episodic Abd. pain	Rt. upper abdomen	Serous	Multilocular	Excision	A & W 2 yr.	Cystic lymphangioma
9	Hoffmann[19]	1965	13 days	M	13 days	Rt. inguinal hernia	Lt. abdomen & rt. ileac fossa	Serous	Multilocular	Marsupialization	A & W 4½ yr.	Cystic lymphangioma
10	Henzel, et al[20]	1966	20	M	36 hr.	Abd. pain frequency of micturition	Pelvis	Serous	Multilocular	Partial excision	A & W 6 mo.	Lymphangioma

TABLE I (*continued*)

CLINICAL DATA OF 21 PATIENTS WITH RETROPERITONEAL LYMPHANGIOMA

S. no.	Author	Year	Age (yr.)	Sex	Duration of symptoms	Symptomatology	Location of tumor	Cyst fluid	Unilocular or multilocular	Treatment	Survival (A = alive; W = well)	Diagnosis
11	Kafka, et al[21]	1970	5/12	M	Few days	Rt. inguinal hernia	Rt. abdomen	?	Multilocular	Excision	A & W 15 mo.	Cystic lymphangioma
12	Singh, et al[22]	1971	4	F	?	Fever, abd. pain	Lt. lower abd.	?	Multilocular	Excision	?	Cystic lymphangioma
13	Peralta, et al[23]	1971	13	M	4 days	Periumbilical colic	Rt. abdomen	Serous	Multilocular	Marsupialization	Survived operation. No follow-up.	Cystic lymphangioma
14	Elhence, et al[24]	1972	10	F	1 mo.	Abdominal pain mass	Rt. ileac fossa	Serous	Unilocular	Marsupialization	A & W 1 mo.	Lymphangioma
15	-do-		28	M	4 mo.	Abdominal pain mass	Rt. lumbar	Serous	Multilocular	Excision	Survived operation. No follow-up.	Lymphangioma
16	-do-		30	F	3 mo.	Abdominal pain mass	Rt. lumbar	?	Multilocular	Excision	Survived operation. No follow-up.	Lymphangioma
17	Oviedo, et al[25]	1972	7	F	1 day	Abdominal pain	Rt. lower abdomen & gluteal	Serous	Multiloculated	Excision	A & W 20 mo.	Cystic lymphangioma
18	Wayne, et al[26]	1973	5	M	1 day	Abdominal pain Fever	Lt. upper abdomen	Sero-sanguinous	?	Excision	Survived operation. No follow-up.	Cystic lymphangioma
19	-do-		6	M	1 day	Abd. pain, fever vomiting	Lt. upper abdomen	-do-	?	Excision	Survived operation. No follow-up	Cystic lymphangioma
20	Castellino, et al[27]	1975	37	F	Asymptomatic		Lt. para aortic	Lymph	Multiloculated	Excision	A & W 3 yr.	Cystic lymphangioma
21	Present case	1976	13	M	3 mo.	Abdominal distention	Mid-abdomen	Sero-sanguinous	Multilocular	Partial excision	A & W 6 mo.	Cystic lymphangioma

3. Focal deposits of lymphoid tissue in the wall.

4. Presence of blood vessels, connective tissue and smooth muscle fibers in the wall.

The morphology of the cyst from the present case fulfilled all the above criteria and thus it can be labeled as cystic lymphangioma.

Lymphangiomas should be differentiated from lymphangiomyomas. Malignant lymphangiomas are known as lymphangiosarcomas. Lymphangiomyomas are predominantly composed of smooth muscle fascicles which are separated by small lymphatic channels. All 28 cases reported up to 1973 have occurred in females and it may be associated with endocrine abnormalities and tuberous sclerosis.[12]

The age at onset of symptoms has ranged from one day to 68 years, with no predeliction for any particular age group. Twenty-five were males and 18 were females. The duration of symptoms varied from one day to 12 years, with a mean of 13.8 months.

Pain was one of the presenting features in about half the cases. Some were mistaken for acute appendicitis, peritonitis or an acute abdomen of unknown cause. A slowly enlarging abdominal mass without pain but a feeling of heaviness was an almost equally frequent complaint. A mass may be discovered as a chance finding on palpation, on plain x-ray film, at surgery or at autopsy.

The pain may be due to obstruction of the intestinal lumen, inflammation, perforation or hemorrhage in the cystic spaces of the tumor. Pressure on the gastrointestinal tract may also cause nausea, vomiting and constipation. Pressure on the urinary tract may produce urinary infection or retention.[13] One patient with a gluteal lymphangioma had fibrinolysis with bleeding.[2]

Lymphangiomas have been classified as capillary, cavernous and cystic. Only the cavernous and the cystic types have been observed in the retroperitoneal region. The capillary lymphangioma consists of an ill-defined mass composed of dilated lymph vessels with a rich cellular connective tissue stroma. It is a compressible growth with a moderate number of channels connecting with the normal adjacent lymphatic system. Cavernous lymphangioma is a spongy compressible tumor with dilated lymph vessels and lymphoid stroma in an actively growing state. There is a moderate number of channels connecting the normal adjacent lymphatic system. Only four cases of retroperitoneal cavernous lymphangiomas have been reported.[9]

Cystic lymphangioma is composed of one or multiple varying sized cysts containing serous, serosanguinous or chylous fluid, with practically no connections with normal adjacent lymphatics.

The etiology is not known. Two theories have been discussed. 1. Acquired, because of obstruction of chylous vessels after inflammation, trauma or degeneration. 2. Congenital, due to proliferation of remnants of the embryonic lymph sac, for unknown reasons.

That the cysts may not have any connection with the lymphatic system is suggested by their slow refilling after aspiration and absence of drainage of chyle after marsupialization or surgery except in one patient.

Total surgical removal is most often employed. Raszowski[14] observed a recurrence seven years later in one case. Marsupialization was employed with good effect in very large tumors.[9] Following a biopsy, two patients were treated with irradiation and showed no signs of recurrence four and seven years later.[9]

It has not been fatal in the cases reported so far except for two deaths due to unrelated causes.[9] Fifteen, however, lacked a follow-up beyond the immediate postoperative period. Twenty-five patients were reported alive and well one month to nine years following surgery.

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Clinical Vignette

The Effect of Imuran on Pancreatic Secretion

A Preliminary Report

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The acute administration of Imuran and hydrocortisone significantly decrease pancreatic flow and protein output in canines. This observed phenomenon may explain the gastrointestinal side reactions encountered in clinical usage of these potent immunosuppresants.

Imuran (azathioprine) is widely used for immunosuppression in a number of diseases with autoimmune manifestations, e.g. Crohn's disease and in organ transplantation, e.g. renal, to prevent rejection. In clinical practice, this cytotoxic agent is frequently administered with corticosteroids, a combination which appears to be synergistic in producing its immunosuppressive effect. Both Imuran and steroids, however, have been reported to incite acute pancreatic inflammation. This investigation was conducted to determine whether or not these drugs as used clinically would adversely affect pancreatic secretion in canines.

METHOD

Two Thomas fistula dogs were prepared and standardized with a continuous infusion of secretin (0.03 U./kg./min.) and CCK-PZ (0.05 U./kg./min.). When the pancreatic flow had reached a plateau, a test bolus of imuran with or without hydrocortisone was administered intravenously. Imuran was given in dosage 100 or 200 mg.; hydrocortisone was injected at 1,000 or 2,000 mg. Following the bolus, pancreatic juice was collected from an indwelling ductal catheter in three 10-minute samples which were analyzed for volume, bicarbonate concentration and protein content. The pancreatic secretion was described in terms of the following parameters: average 10′ flow (ml./10′), maximum bicarbonate concentration (mEq./l.), bicarbonate output (mEq./10′), average protein concentration (mg.%) and average protein output (mg./10′). These secretory parameters were compared with similar data obtained from three 10 minute collections prior to the test bolus.

RESULTS

The secretory data are presented in Table I. It is clear that the bolus administration of 100 or 200 mg. of Imuran alone did not alter flow, bicarbonate, or protein response in the stimulated pancreas. The addition, however, of hydrocortisone in 1,000 or 2,000 mg. dosage to the Imuran

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TABLE I

PANCREATIC SECRETION DATA BEFORE AND AFTER THE ADMINISTRATION OF IMURAN WITH AND WITHOUT HYDROCORTISONE

	No.	Average flow ml./10′	Average max. HCO_3 mEq./l.	Average HCO_3 output mEq./10′	Average protein conc. mg.%	Average protein output mg./10′
Control	4	11.8 ± 0.2	128 ± 1.7	1.43 ± 0.02	18.1 ± 1.5	220.7 ± 18.5
Imuran 100 mg.		11.9 ± 0.3	131 ± 0.6	1.49 ± 0.02	16.8 ± 0.8	216.1 ± 12.7
Control	4	12.0 ± 0.4	128 ± 1.7	1.52 ± 0.06	16.3 ± 0.7	208.7 ± 13.3
Imuran 100 mg.		10.4 ± 0.4*	130 ± 1.4	1.40 ± 0.05	15.2 ± 0.6	160.6 ± 10.1*
+ Hydrocortisone 1,000 mg.						
Control	2	11.3 ± 0.1	138.3 ± 1.2	1.45 ± 0.83	15.3 ± 0.3	172.3 ± 10.4
Imuran 200 mg.		11.2 ± 0.1	133 ± 1.5	1.42 ± 0.92	16.1 ± 0.5	181.1 ± 11.2
Control	2	12.8 ± 0.4	123 ± 1.1	1.56 ± 0.64	13.3 ± 0.3	171.1 ± 9.4
Imuran 200 mg.		10.9 ± 0.2	118 ± 2.3	1.52 ± 0.27	12.0 ± 1.0	135.9 ± 12.1*
+ Hydrocortisone 2,000 mg.						

Data given as mean ± standard error.
* Denotes statistical significance $P < 0.05$.

produced a statistically significant inhibition of flow and protein output. In no experiment did maximum bicarbonate concentration or output appear to be affected.

COMMENT

The data clearly indicate that a combination of Imuran and hydrocortisone administered as a bolus to dogs at dosage comparable to clinical usage is capable of suppressing pancreatic flow and enzyme secretion. It is possible, therefore, that this phenomenon may occur in man and be responsible, at least in part, for gastrointestinal side reactions observed with these drug regimens. Before this hypothesis can be accepted, however, it is necessary to study the effects of repeated administration and, of course it would be desirable to study patients before and after courses of the drugs.

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The Radiology Corner*

SPONTANEOUS PNEUMOPERITONEUM WITH *Pneumatosis Cystoides Intestinalis* IN A PATIENT WITH MIXED CONNECTIVE TISSUE DISEASE

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Pneumatosis cystoides intestinalis (PCI), a disorder in which gas filled cysts develop within the bowel wall, has been associated with collagen vascular disease, usually progressive systemic sclerosis (PSS). We have extended the spectrum of collagen vascular disease associated with PCI by this report of a patient with mixed connective tissue disease (MCTD) who developed PCI and recurrent spontaneous pneumoperitoneum (SP). Possible pathogenetic mechanisms are reviewed and the management of the asymptomatic patient with pneumoperitoneum, PCI and collagen vascular disease is discussed.

Pneumatosis cystoides intestinalis is a disorder of the gastrointestinal tract in which gas filled endothelial lined cysts develop within the wall of the small and occasionally the large bowel. Approximately 85% of cases are associated with other lesions of the gastrointestinal tract, the most common of which is duodenal ulcer.[2] Other disorders that have been associated with PCI include obstructive lung disease, gastric malignancy, inflammatory bowel disease and intestinal obstruction of varied etiologies, e.g. volvulus and diverticulitis. In 1966, Hughes, et al[3] reported the first case of PCI in a patient with progressive systemic sclerosis (PSS). Since that communication, 17 other cases of PCI in patients with collagen-vascular disease have been reported.[4] With the exception of two patients with rheumatoid arthritis (one of whom also had a fecal impaction with consequent intestinal obstruction) and one with dermatomyositis, all these patients have had PSS. The following case report extends the spectrum of collagen-vascular diseases associated with PCI to include the recently described mixed connective tissue (MCT) disease syndrome[5] and stresses the importance of considering PCI in the differential diagnosis of pneumoperitoneum.

CASE REPORT

The patient is a 60-year old white female who was first admitted to Montefiore Hospital and Medical Center in November, 1972 for evaluation of dysphagia and proximal muscle weakness of the arms and legs associated with myalgias and parasthesias. She had a history of Raynaud's phenomenon with recent tightening of the skin in the hands. Work-up at that time revealed a hematocrit of 36%, sedimentation rate of 85 mm./hr., positive ANA (speckled

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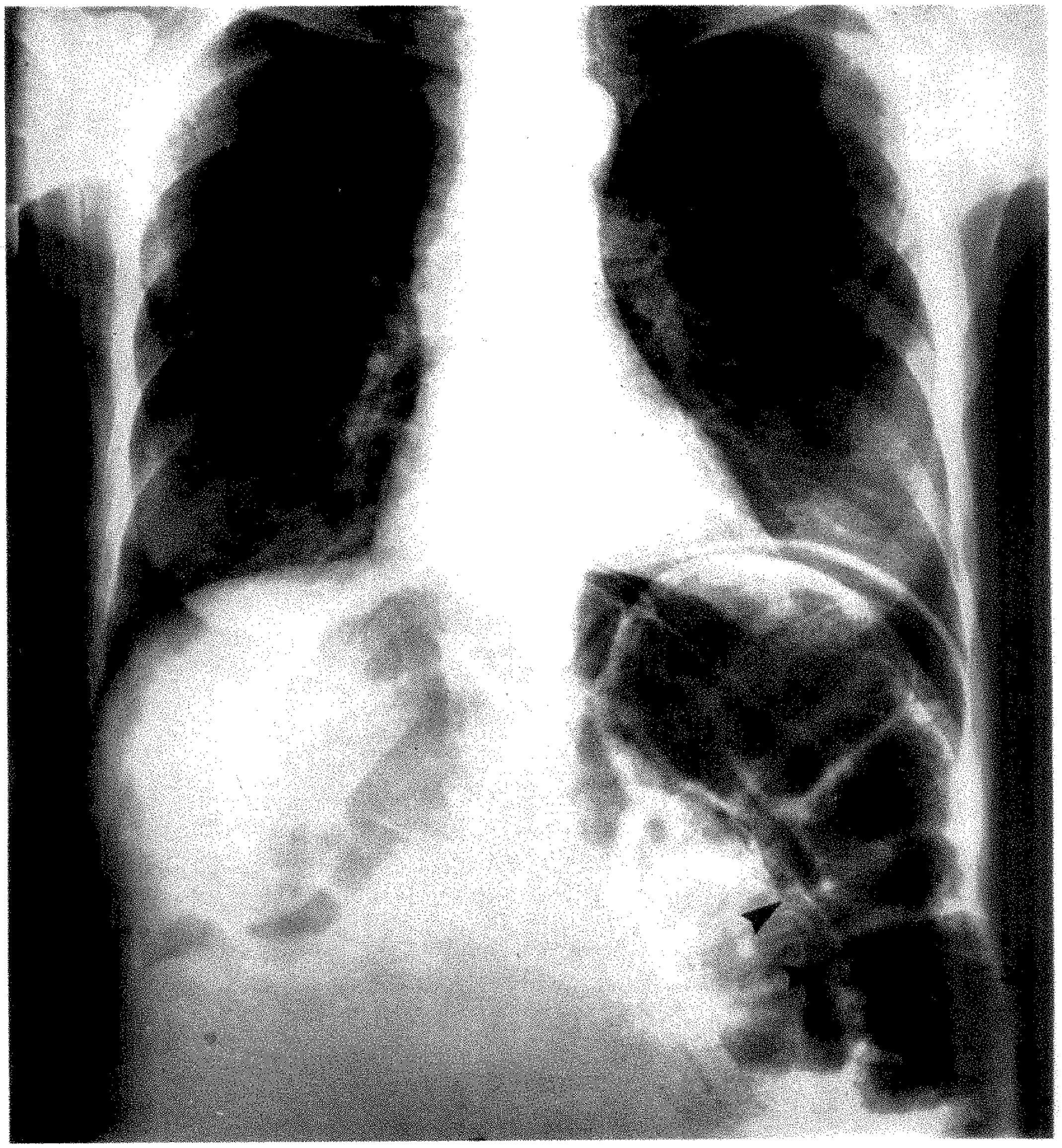

Fig. 1—Chest x-ray revealing free air under the left hemidiaphragm; gas filled cysts in the wall of the jejunum are also seen (marked by arrows).

pattern), negative latex fixation and a normal serum protein electrophoresis. CPK was 2,175 I.U./l.; LDH, 825 I.U./l.; SGOT, 174 I.U./l. BUN and creatinine were normal. An upper gastrointestinal series was normal although motility testing revealed decreased peristaltic activity throughout the body of the esophagus. Barium enema and intravenous pyelography were unremarkable. Electromyography was suggestive of myopathy although a muscle biopsy was reported as normal. Chest x-ray revealed no parenchymal disease and no free air under the diaphragm. Pulmonary function tests were not performed. The patient had features of both dermatomyositis and scleroderma suggesting the diagnosis of mixed connective tissue disease and was

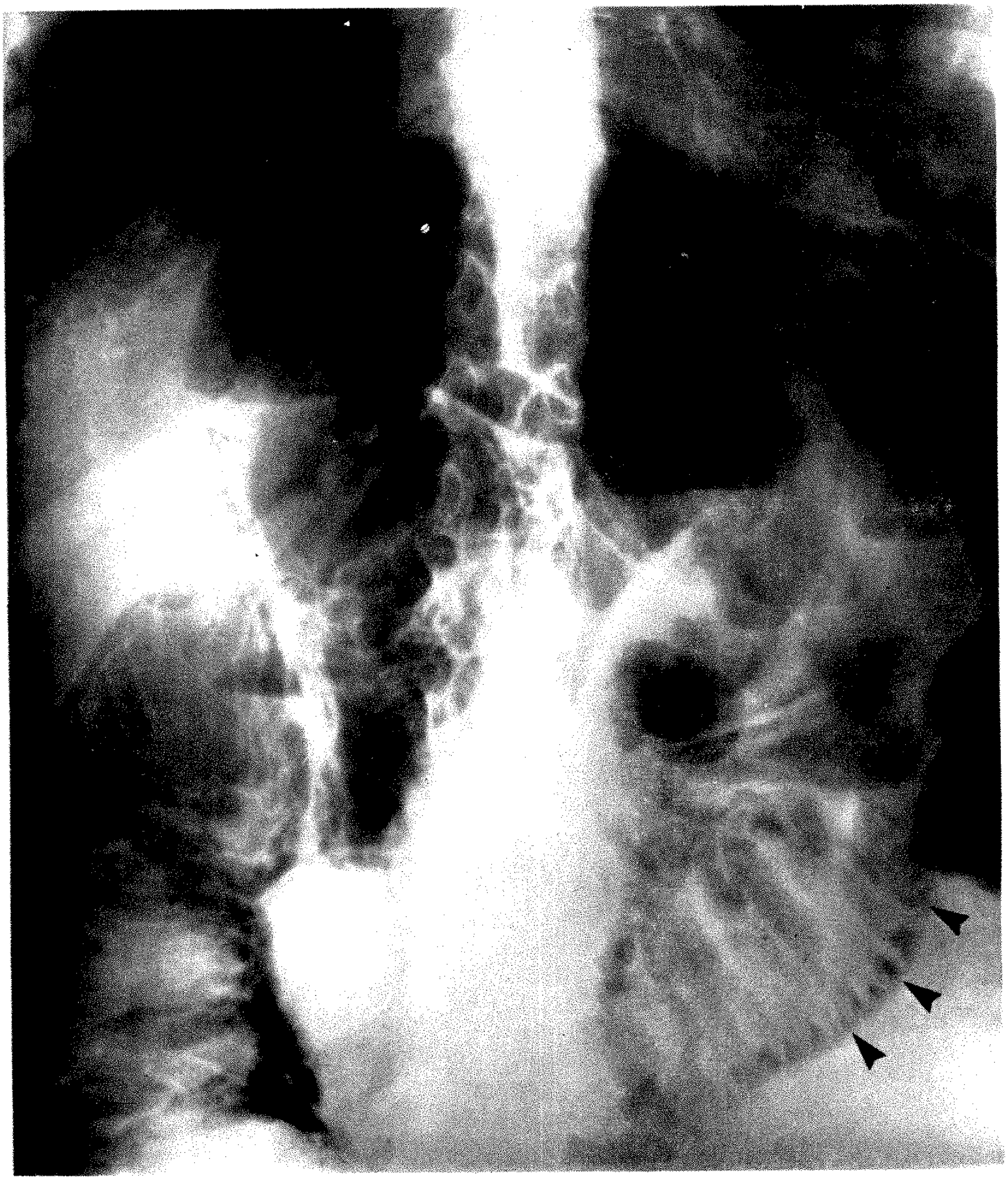

Fig. 2—An upright abdominal x-ray demonstrating a nonspecific ileus pattern with gas filed cysts throughout the wall of the small bowel (marked by arrows).

treated with prednisone, 30 mg. P.O. daily. Subsequently her weakness lessened, the skin on her hands became looser and the CPK decreased to 600 I.U./l.

She remained improved and stable until November, 1975, when she was readmitted for abdominal distention, epigastric pain, vomiting and diarrhea. A chest

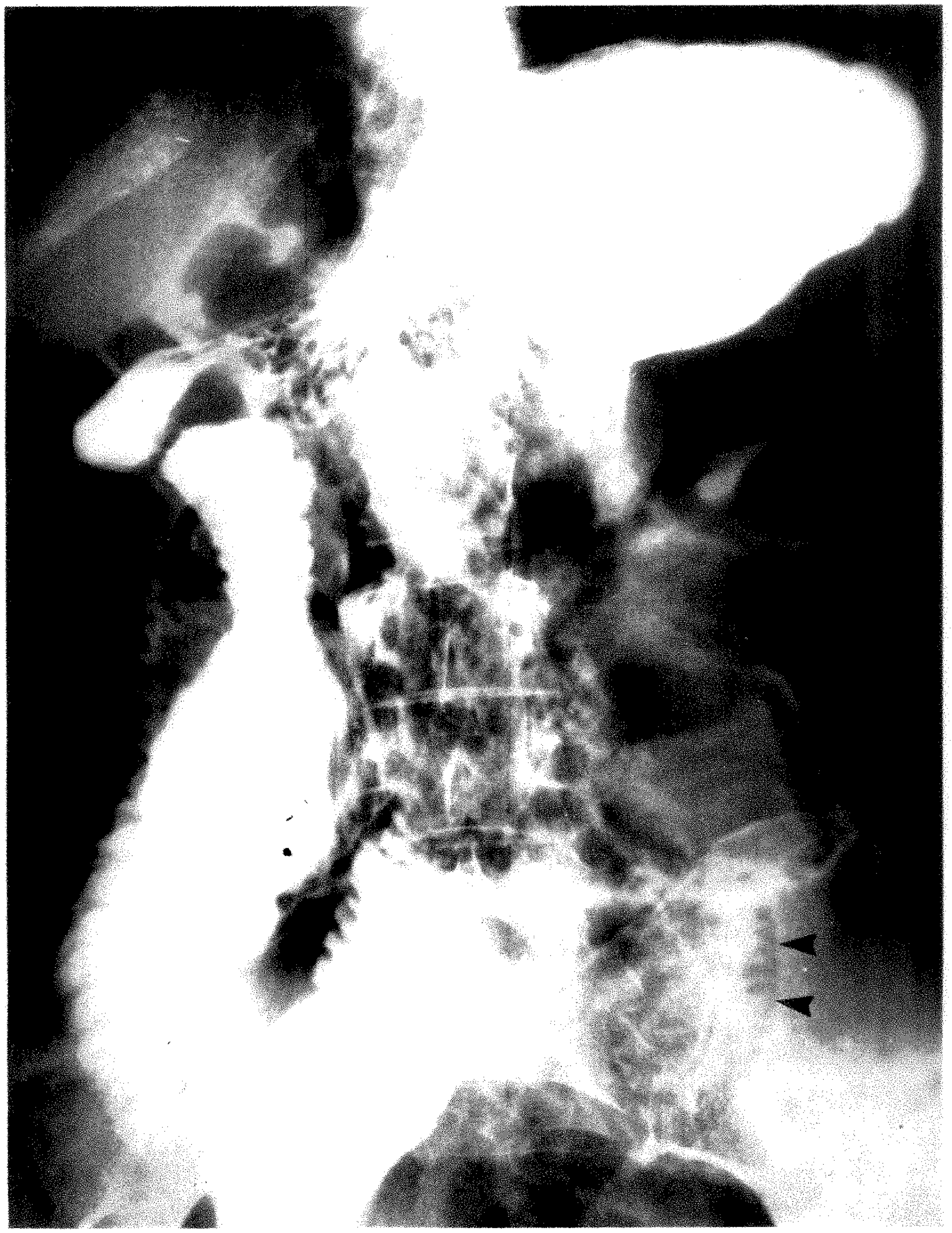

Fig. 3—An upper gastrointestinal series revealing a dilated duodenum and proximal small bowel. Gas filled cysts are present in the jejunum and ileum (marked by arrows).

x-ray revealed free air under the left hemidiaphragm (Fig. 1) but no parenchymal lung disease. An obstructive series showed a nonspecific ileus pattern with gas-filled cysts (Fig. 2) throughout the wall of the small bowel. A surgical consultant recommended surgery at that time. Because, however, of the appreciated association among PCI, pneumoperitoneum and collagen-vascular disease, the patient was treated supportively with I.V. hydration and decompression via a long tube connected to intermittent suction. An upper gastrointestinal series (Fig. 3) subsequently revealed a dilated esophagus without a distal stricture and a dilated duodenum and small bowel with *pneumatosis cystoides* of the jejunum and ileum. A malabsorption work-up revealed a fecal fat of 0.53 gm./24 hours; normal prothrombin time, calcium, phosphorus, B_{12} and folate; serum carotene of 22 μg.% and a d-xylose excretion of 4.3 gm./24 hours. Excretion of urinary indican was 267 mg./24 hr. Culture of a duodenal aspirate revealed 5×10^5 aerobic and less than 10^3 anaerobic organisms/ml. The patient was treated with tetracycline, 250 mg. P.O., q.i.d. and the diarrhea, vomiting and abdominal distention lessened. Other laboratory data at that time included a 4+ positive ANA and positive ENA in a titer of 1:250, which further supported the diagnosis of mixed-connective tissue disease. During that admission, the patient had several episodes of partial small bowel obstruction accompanied by free air under the diaphragm, all of which resolved spontaneously. The dose of prednisone was increased to 60 mg. P.O. daily with decrease in the frequency of obstructive episodes.

During the year prior to the present admission, the patient's weight decreased from 41.5-37 kg. She complained of progressive proximal muscle weakness and three to five loose bowel movements daily without blood or mucus. At the time of her present admission, she was receiving Ampicillin, 250 mg. P.O. q.i.d. and prednisone, 10 mg., alternating with 15 mg. daily.

On physical examination, the patient was a cachetic female in no acute distress with normal vital signs. A mask-like facies with tight skin around the mouth and pursed lips was noted. No icterus or adenopathy was present. The lungs were clear to percussion and auscultation and examination of the heart revealed a 2/6 systolic murmur. The abdomen was distended and tympanitic without masses, organomegaly, tenderness, succussion splash or bruit. Neurologic examination revealed marked proximal muscle weakness without tenderness and with normal sensation. Laboratory data included a hematocrit of 30%; WBC, 7,500; sedimentation rate of 73 mm./hr. prothrombin time, 10/10 sec. SMA 6 was normal. The total protein was 5.8 gm.% with an albumin of 2.8 gm.%. SGOT, 26 I.U./l.; CPK, 66 I.U./l. and serum carotene 53 μg.%. Chest x-ray again showed no parenchymal disease but revealed free air under the diaphragm and dilated loops of small bowel with *pneumatosis cystoides*. ANA was 3+ positive (a speckled pattern), latex fixation was negative. ENA was not reported.

It was thought that the patient might be suffering from a steroid myopathy in view of the marked weakness with normal enzymes. The dose of prednisone was reduced. The pneumoperitoneum again resolved spontaneously, although the weakness persisted. After one week, she was discharged at her own request to be followed-up by her private physician.

COMMENT

The etiology of PCI remains undefined. Currently the most widely accepted theory involves mechanical factors, i.e. a break in intestinal mucosal integrity with increased intraluminal pressures, forcing intestinal gas to dissect into the bowel wall. This allows an understanding of the occurrence of PCI and most of its associated disorders. Keyting, et al,[6] after noting the occurrence of PCI in three patients with chronic obstructive lung disease, demonstrated in dogs that air can dissect along the bronchi into the mediastinum, pass into the retroperitoneum and finally dissect along vascular channels into the bowel wall. They concluded that alveolar rupture with gas dissection was often pathogenic in PCI. Hughes[3] thought that the lung disease in his one patient with scleroderma, even though restrictive and not obstructive as in his other patients, was responsible for the development of PCI. Lung involvement is common in PSS and restrictive lung disease has recently been reported in 50% of patients with MCT disease. Restrictive lung disease, however, probably does not cause alveolar rupture and indeed our patient developed PCI without any clinically significant lung disease. Thus alveolar rupture is unlikely to be the source of the gas cysts in our patient or the other reported patients with PCI and PSS. More likely to be responsible is the disordered small bowel motility in these patients, along with stasis, bacterial overgrowth and partial small bowel obstruction.

Some authors, notably Meihoff, et al,[8] have stressed the gravity of finding PCI in PSS, whereas others have found it of less dire prognostic significance.[4] Meihoff felt that the occurrence of PCI *per se* was not so important but that its appearance implied the overall process had neared an end-stage. Mueller, et al[4] in their review of the literature, however, did not find this to be true in all cases. There does not appear to be a predictable time course between the occurrence of PCI and death. Our patient has done relatively well for the one year since the development of PCI and her present difficulties possibly are due more to side-effects of therapy than to her basic disease process. This may be due to the somewhat better prognosis of those with MCT as opposed to PSS, in which renal involvement is more common and severe.[7] It would appear that the prognosis of PCI and collagen-vascular disease, as with other PCI associated disorders, remains that of the underlying disease.

Lastly, the need for caution in reflexly recommending surgery in a patient with known collagen vascular disease that develops free air under the diaphragm is to be emphasized. Our patient, as Meihoff's second patient did, almost underwent explorative surgery for perforated viscus on the basis of a small bowel obstructive pattern and free air under the diaphragm. Her lack of symptoms and signs were automatically attributed to steroid therapy. The presence of free air in a patient with PSS or other collagen disease, especially in the absence of peritoneal signs, should at least suggest the diagnosis of PCI. If this diagnosis is confirmed, the patient may then be managed medically without immediate operative intervention. •

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The Last Page

QUESTIONS IN GASTROENTEROLOGY

MICHAEL RUOFF, M.D., F.A.C.G.*
New York, N. Y.

The Last Page appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page,* again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. CONCERNING ISOAMYLASES:

A. The pancreatic (P) type arises only in the pancreas.

B. The salivary (S) type arises in many tissues in addition to the salivary glands and pancreas.

C. S type iseoamylase may be elevated post-abdominal surgery, opiates, acute alcohol intake and in patients with lung cancer.

D. The principal serum isoamylase is the P type.

(Page 421)

2. CONCERNING TESTS FOR ACUTE PANCREATITIS:

A. Positive (raised) amylase to creatinine clearance ratios are found in 90% of patients with hyperamylasemia that have acute pancreatitis.

B. False positive clearance ratios occur in patients with diabetic ketoacidosis or burns.

C. The ratio of urinary amylase to urinary creatinine is increased during acute pancreatitis from a mean of 2.6 to a mean of 51.

D. The ratio of urinary amylase to urinary creatinine is normal in cases of macroamylasemia and S-type hyperamylasemia.

(Page 423)

3. PANCREATIC ENZYME INHIBITORS:

A. Are released by the pancreas.

B. Can be estimated by comparing enzyme activity of whole serum to that of dilute serum.

C. Are decreased by the administration of glucocorticoids.

D. Are increased by high protein diets and anabolic steroids.

(Page 433)

4. IN USING B-SCAN ULTRASONOGRAPHY IN THE DIAGNOSIS OF LIVER CANCER:

A. Cancer is represented by irregularity of echos and increased intensity of irregular echos.

---

* Assistant Professor of Clinical Medicine, New York University School of Medicine.

B. Diagnostic correlations can be drawn between the ultrasonic patterns and serum alpha-fetoprotein levels.

C. False positive results tend to occur in patients with cirrhosis.

D. The resolution of focal lesions (2 cm.) is similar to that obtained with scintigraphy.

(Page 440)

5. IN ACUTE ALCOHOLIC HEPATITIS:

A. Corticosteroids do not reduce mortality.

B. If there is no contraindication for liver biopsy, mortality rates are below 20%.

C. If percutaneous liver biopsy cannot be done due to prothrombin time elevation mortality is 70-100%.

D. In the high risk group that cannot be biopsied, those with the most prolonged prothrombin times have the worst prognosis.

(Page 447)

6. HERELLEA (*ACINETOBACTER*):

A. Are gram positive spore forming anaerobes.

B. Hydrolyze bile salts.

C. Deconjugate bile salts.

D. Can be present in high numbers in the jejunum of patients with gastric resection.

(Pages 451, 452)

7. CONCERNING *VIBRIO CHOLERAE:*

A. Aboral contact in dogs produces fulminant canine cholera.

B. *Vibrio cholerae* is not affected by gastric acid so it is easy to explain how oral ingestion can account for the presence of vibriocidal titers in most of an exposed population by the age of puberty.

C. In many developing countries it is customary to wash or immerse the anal area in surface water after defecation.

D. Anal or rectal application in dogs will induce significant increases in the titer of serum vibriocidal antibody.

(Page 455)

8. PATIENTS WITH BARRETT'S ESOPHAGUS MAY PRESENT WITH:

A. Mid esophageal strictures.

B. Distal esophageal strictures.

C. Distal esophagitis.

D. Esophageal ulcers.

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9. MUCOEPIDERMOID CARCINOMA OF THE ESOPHAGUS:

A. Occurs in the upper esophagus.

B. Originates from esophageal glands.

C. Is invasive and metastatic.

D. Is another name for the adenosquamous cell carcinoma occurring at the esophagogastric junction.

(Pages 468, 469)

10. IN SCLERODERMA:

A. Esophageal abnormalities, at least early in the disease, may be due to abnormal function rather than to changes in structure and therefore may be reversible.

B. Early aggressive antireflux therapy unfortunately does not modify the progression of the esophageal disease.

C. The upper (striated) esophagus shows simultaneous contractions and reduced sphincter pressure.

D. Thirty per cent of patients have motor abnormalities of the esophagus and lower esophageal sphincter if manometry is employed in their evaluation.

(Page 476)

11. CONCERNING MERCURY INTOXICATION:

A. If mercury is found in the urine it means that toxic levels have developed in the kidney and brain.

B. To effect systemic absorption of mercury, metallic mercury must be converted to divalent mercury (mercuric ion).

C. Free metallic mercury usually passes through the gut rapidly enough to preclude significant conversion to divalent mercury.

D. Enterocolitis and tremor are clinical manifestations of systemic mercury toxicity.

(Page 479)

12. CALCIFIED MUCINOUS ADENOCARCINOMA OF THE STOMACH:

A. Occurs if the patients have associated hyperparathyroidism.

B. Tends to occur in a younger age group.

C. Shows a uniform distribution of calcification throughout the tumor.

D. Is extraordinarily rare with only three cases in the published literature.

(Page 483)

13. CONCERNING LYMPHANGIOMAS:

A. About one-third occur in the neck and are known as cystic hygromas.

B. Those involving the retroperitoneum connect to the lymphatic system and rapidly fill after aspiration.

C. If abdominal in location are only seen following traumatic blockage of chylous vessels.

D. If malignant are known as lymphangiosarcomas.

(Page 489)

14. IMURAN ADMINISTRATION TO DOGS:

A. Does not affect the stimulated pancreas.

B. If combined with hydrocortisone suppresses pancreatic flow and enzyme secretion.

C. Given with hydrocortisone reduces the maximum bicarbonate concentration and output.

D. Invariably causes fulminant acute hemorrhagic pancreatitis.

(Page 491)

15. *PNEUMATOSIS CYSTOIDES INTESTINALIS:*

A. Is associated with progressive systemic sclerosis and mixed connective tissue disease.

B. Causing a pneumoperitoneum should be managed surgically.

C. Is always due to obstructive lung disease causing alveolar rupture and gas dissection.

D. In 85% of cases is associated with other lesions of the gastrointestinal tract, the most common of which is duodenal ulcer.

(Page 499)

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

Progress in Surgery, Vol. 15: edited by M. Allgower, M.D., S. E. Bergentz, M.D., R. Y. Calne, M.D. and U. F. Gruber, M.D. 159 pages, illustrated. S. Karger, AG, Basel, Switzerland, 1977. Price $28.75.

This is an interesting addition to the series *Progress in Surgery* with contributions mainly from Germany and England. There are two introductory chapters on management of the patient in the Intensive Care Unit with one devoted to patients undergoing or following abdominal surgery. The yearly mortality in the latter group, including patients with gastrointestinal hemorrhage, cirrhosis and pancreatitis, averaged about 30%. There is an interesting paper on the value of colloidal solutions in hypovolemia and another on anatomic changes in the antropyloric wall in gastric ulcer disease. Finally, there is a valuable contribution to the surgical literature in which the authors from the University of Munich show the value of the laser in the control of hemorrhage in gastrointestinal bleeding. They successfully controlled 131 of 140 bleeding incidents in 106 patients during the period September, 1975-1976.

There are a wide variety of papers in this small volume and gastroenterologists, internists and surgeons will benefit from some of the latest clinical advances on the continent of Europe.

David A. Dreiling, M.D., F.A.C.G.

Modern Topics in Gastrointestinal Endoscopy: edited by K. F. R. Schiller, M.D. and P. R. Salmon, M.B. 342 pages, illustrated. Year Book Medical Publishers, Chicago, IL, 1977.

Despite the large number of books which have been published on endoscopy over the last few years this British book, with 25 different contributors from various parts of England and occasional chapters from German and American experts, proves to be an excellent introductory book to the subject. It covers almost every known aspect of endoscopy from the history of instrumentation to the most recently developed sophisticated endoscopic technics. The chapter on the history of endoscopy by D. D. Gibbs is an interesting description of how endoscopy came into being. The physics of fiberoptic endoscopy by Hopkins is a sophisticated and complex discussion of physics and light relation to endoscopy. The development of the endoscope was largely dependent upon an understanding of transmission of light to a distant area along a fiberoptic tube. Thereafter there are chapters discussing esophagoscopy, gastroduodenoscopy, enteroscopy and colonoscopy as well as pancreatography. Almost without exception the chapters are excellent and the emphasis on understanding and interpreting pathology is consistently stressed throughout this volume. Laparoscopy is also considered.

All chapters are comprehensive and although one might state that today it is impossible to cover such a wide range of topics in one volume, this volume has succeeded in doing this within the limits of the space available. The final two chapters are devoted to the possibilities of research by Dr. Truelove and a postscript by the authors, Schiller and Salmon. The former points out that the use of endoscopy has far outstripped the basic research carried out by endoscopists and the latter discusses the objectives and major conclusions of each chapter in relation to the book as a whole. All in all this is an excellent book for gastroenterologists and surgeons wishing to have an over all view of endoscopy, its development and its present status in gastroenterology.

Adrian J. Greenstein, M.D., F.A.C.G.

Essential Hepatology: by Thomas S. Chen, M.D. and Peter S. Chen, M.D. 360 pages, illustrated. Butterworths, Woburn, MA, 1977. Price $24.50.

As reflected in the title, this book is an introduction to hepatology. The concise and clear text should be useful to medical students and physicians who wish to acquire an overview in liver disorders.

The adoption of standardized hepatologic nomenclature established recently by the International Association for the Study of the Liver and the World Health Organization is helpful in defining more precisely the various disease entities.

Over all, this is a useful and up-to-date book in the basics of liver disease.

Demetrius Pertsemlidis, M.D., F.A.C.G.

Solid Liver Tumors, Major Problems in Clinical Surgery—Vol. XXII, 1st ed.: by James H. Foster, M.D. and Martin M. Berman, M.D. 342 pages, illustrated. W. B. Saunders Co., Philadelphia, PA, 1977. Price $18.00.

This book draws attention to recent progress in the diagnosis and surgery of primary and metastatic liver tumors. It reflects a serious effort to accumulate data and define directions for guidance of the surgeons to cope with the difficulties of liver resections.

The authors have tried successfully to present a complete review of the subject of liver tumors in a commendable and admirable way.

The book is highly recommended as most valuable for surgeons and hepatologists.

Demetrius Pertsemlidis, M.D., F.A.C.G.

Critical Surgical Care: edited by John S. Najarian, M.D. and John P. Delaney, M.D. 671 pages, illustrated. Stratton Intercontinental Medical Book Corporation, New York, NY, 1977. Price $29.95.

Critical Surgical Care, edited by Najarian and Delaney is comprised of selected papers and discussions from the Annual Continuation Course in Surgery given by the University of Minnesota. There are some 53 lectures given by the Who's Who in Surgery and grouped into five sections viz: emergency treatment, specific organ injury, systemic responses and complications of trauma, infections and burns. The series in well conceived and should serve as a textbook for surgical clerkship or for study for Boards.

David A. Dreiling, M.D., F.A.C.G.

Malabsorption, Major Problems in Internal Medicine—Vol. XIII, 1st ed.: by Marvin H. Sleisenger, M.D. and Lloyd L. Brandborg, M.D. 261 pages, illustrated. W. B. Saunders Co., Philadelphia, PA, 1977. Price $14.00.

Considering the large number of recent publications on malabsorption this book is particularly useful in being limited to 261 pages and covering most of the important aspects of the physiology of normal absorption, the clinical and pathophysiological features of malabsorption and the laboratory diagnosis, of the entity. Subsequent chapters consider the immunology and bacteriology of the gastrointestinal tract. Following this is a chapter on malabsorption syndromes in children which considers particularly cystic fibrosis and various other abnormalities of amino acid malabsorption. Chapter 9 considers in detail the classification of the malabsorption syndrome. Seven categories of disease are discussed including defective intraluminal hydrolysis, mucosal cell abnormality, lymphatic obstruction, multiple defects, infective causes, drug-induced malabsorption and unexplained causes of malabsorption. This is an excellent review of this group of malabsorptive syndromes and will be of value to students studying gastroenterology, as well as to those practicing gastroenterology, internal medicine and surgery.

Adrian J. Greenstein, M.D., F.A.C.G.

Computerized Axial Tomography: by J. Gambarelli, G. Guerinel, L. Chevrot and M. Mattei. 286 pages, illustrated. Springer-Verlag New York Inc. New York, NY, 1977. Price $105.60.

Cross-Sectional Anatomy, Computed Tomography and Ultrasound Correlation: by Barbara L. Carter, M.D., James Morehead, Ph.D., Samuel M. Wolpert, M.B., Steven B. Hammerschlag, M.B., Harry J. Griffiths, M.D. and Paul C. Kahn, M.D. Illustrated. Appleton-Century-Crofts, New York, NY, 1977. Price $42.50.

Have CAT and Sonography scans got you down? Do they all look like gobbledegook to you? Well here are two excellent text atlases which correlate anatomic sections with scan reproductions. There is no question that the Gambarelli volume is more lush, presenting colored as well as black and white sections but then it is twice as expensive. Frankly $105 is much. Either book will do very well to enable you to face a CAT or Sonoscan with equanimity.

David A. Dreiling, M.D., F.A.C.G.

Gastroenterology Specialty Board Review: by William A. Sodeman, Jr., M.D. and Thomas A. Saladin, M.D. 177 pages. Medical Examination Publishing Co., Inc., Flushing, NY, 1977. Price $12.00.

This is a useful book for those preparing for Gastroenterology Board Examinations. The questions are completely referenced to enable the reader to review the subject, when necessary.

Demetrius Pertsemlidis, M.D., F.A.C.G.

World Review of Nutrition and Dietetics, Vol. 27, Some Aspects of Human Nutrition: edited by G. H. Bourne. 178 pages, illustrated. S. Karger AG. Basel, Switzerland, 1977. Price $49.50.

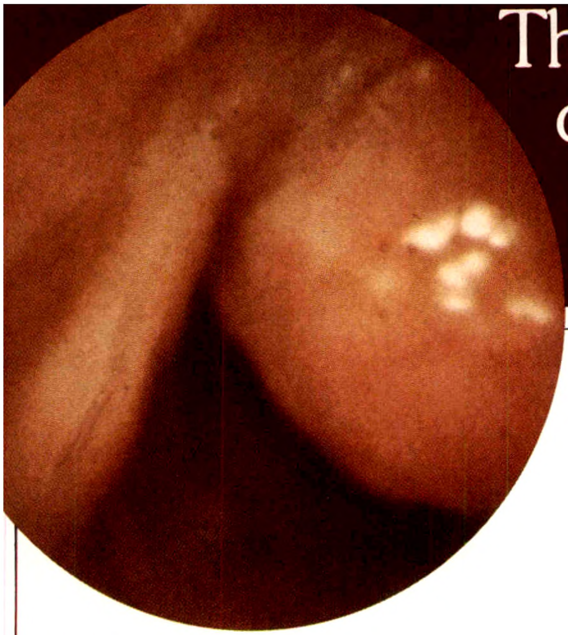
Some Aspects of Human Nutrition covers the following topics: 1. Nutrition of the preschool child in India. 2. Perspectives in dietary fiber in human nutrition. 3. Formulation and evalulation of meals based on locally available foods for young children. 4. Possible role of hydrolysis products of the dietary components in the mechanisms of the exocrine pancreatic adaptation to the diet. 5. Pangamic acid (Vitamin B_{15}), a review.

I found 2, 4 and 5 most interesting. Since I am merely a surgeon, I am sure the gastroenterologists will encounter much valuable information in this brief but much needed update on factors nutritional.

David A. Dreiling, M.D., F.A.C.G.

The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing.
X-ray studies are inconclusive.



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Esophagoscopy was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

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Final classification of the less-than-effective indications requires further investigation.

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***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

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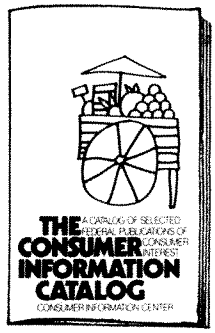
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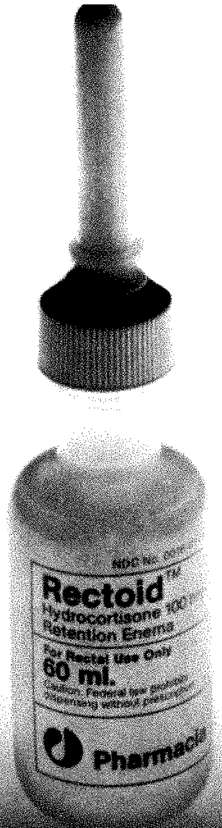

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WARNINGS: Prolonged use may cause systemic reactions. Do not delay needed surgery while awaiting response to medical treatment. Proper insertion of the enema tip is essential to prevent rectal wall damage. Increased dosages are indicated before, during and after unusually stressful situations. Signs of infection may be masked, and new infections may appear, along with decreased resistance and decreased ability to localize infection.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Adequate human reproduction studies have not been done with corticosteroids. In pregnancy, nursing mothers or women of childbearing potential, weigh the possible benefits of the drug against the possible hazards to the mother and the embryo or fetus. Observe infants born of mothers treated during pregnancy for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention and increased excretion of potassium, requiring dietary restrictions and supplementation, may occur. All corticosteroids increase calcium excretion. *Immunization procedures, especially against smallpox, should not be undertaken in patients receiving corticosteroids, because of the possible hazard of neurological complications and lack of antibody response.* Close observation and chemoprophylaxis are indicated in patients with latent tuberculosis or tuberculin reactivity.
PRECAUTIONS: Use with caution in cases of impending perforation, abscess or other pyogenic infection, fresh intestinal anastomoses, obstruction, extensive fistulas, and in the presence of active or latent peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis, or myasthenia gravis. Surgical prognosis may be impaired by increased infection hazard. Administer larger dose of appropriate antibiotics if infection is suspected. Drug-induced secondary adrenocortical insufficiency, minimized by a gradual dosage reduction, may occur with prolonged therapy. This condition may persist for months after discontinuation of therapy; therefore, hormone therapy should be reinstituted during periods of stress. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Corticosteroids exhibit an enhanced effect in patients with hypothyroidism and cirrhosis and should be used cautiously in patients with ocular herpes simplex because of possible cornea perforation. Use the lowest possible dose to control the condition and institute a gradual dosage reduction as soon as possible.

Psychic derangement may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.
ADVERSE REACTIONS: Local pain or burning, rectal bleeding, and apparent exacerbations of the disease or sensitivity reactions may occur in rare instances. The following adverse reactions should be kept in mind whenever corticosteroids are given.

Fluid and Electrolyte Disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurological:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state, suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus; increased requirement for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
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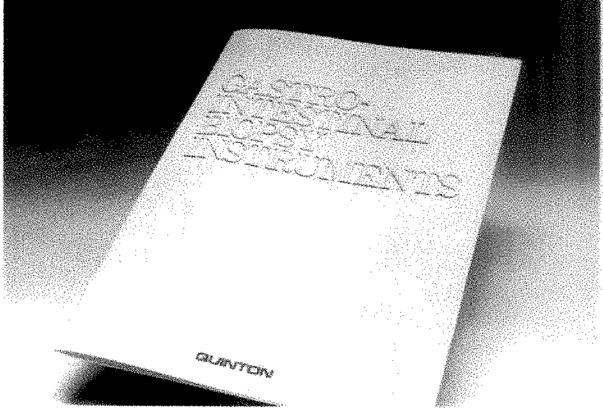

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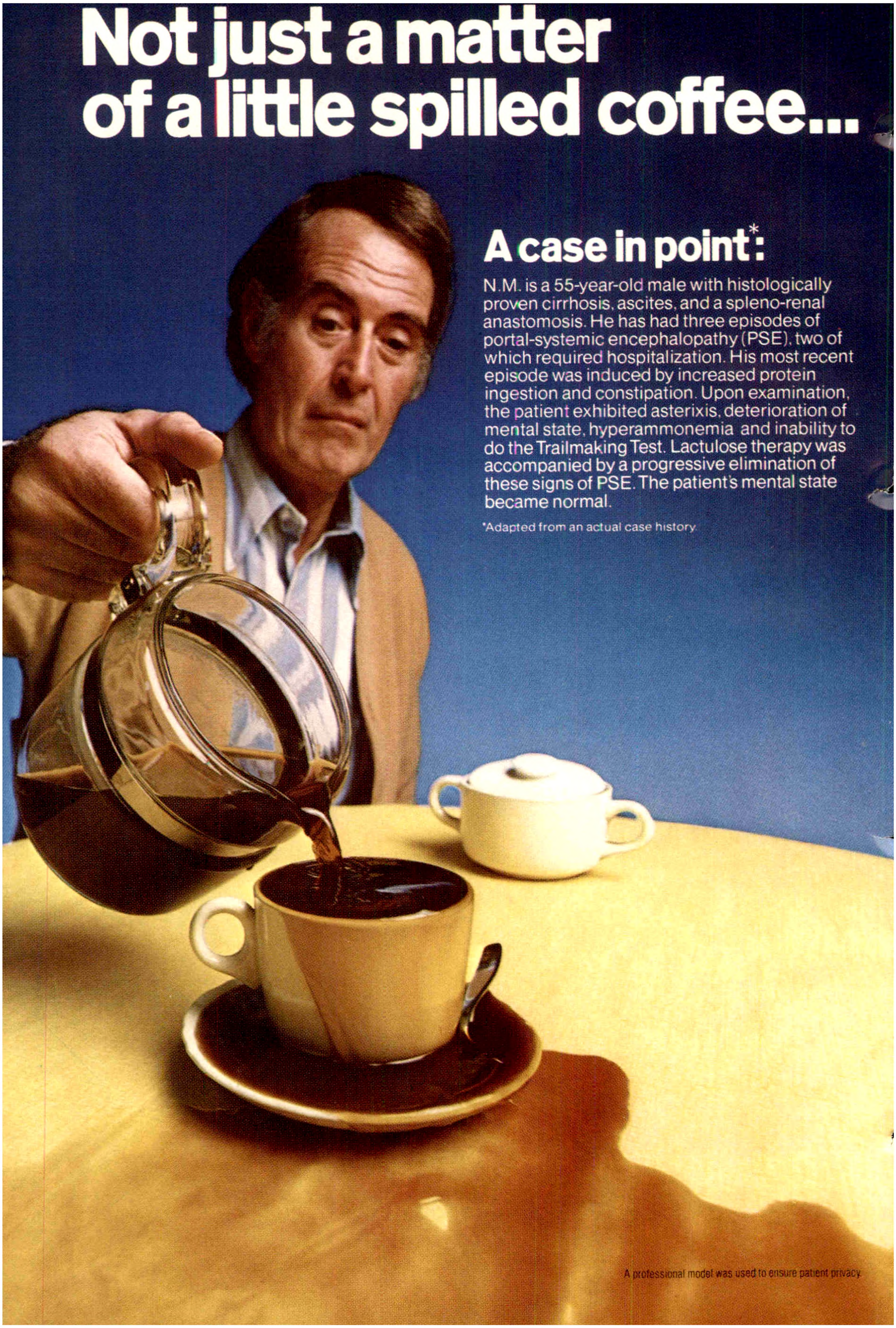

A case in point*:

N.M. is a 55-year-old male with histologically proven cirrhosis, ascites, and a spleno-renal anastomosis. He has had three episodes of portal-systemic encephalopathy (PSE), two of which required hospitalization. His most recent episode was induced by increased protein ingestion and constipation. Upon examination, the patient exhibited asterixis, deterioration of mental state, hyperammonemia and inability to do the Trailmaking Test. Lactulose therapy was accompanied by a progressive elimination of these signs of PSE. The patient's mental state became normal.

*Adapted from an actual case history.

A professional model was used to ensure patient privacy.

..this is portal-systemic encephalopathy (PSE)–

(Also called Hepatic Encephalopathy, Hepatic Coma.)

–a common complication of chronic liver disease.

Suspect PSE in every patient with cirrhosis.

Common early symptoms

- irritability
- euphoria
- lack of concern for others
- inappropriate behavior
- faraway look
- inversion of sleep pattern

Results of recent investigations of PSE

- Two-thirds of cirrhotic patients with portal hypertension who appeared mentally normal by conventional assessment revealed impairment of cerebral function on psychomotor testing. This dysfunction was in the same range as that in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

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Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose die

WARNINGS: *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

References:
1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.
2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non-cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.
3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metal olism. Gastroenterology 72:1119, 1977.

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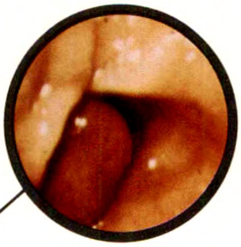

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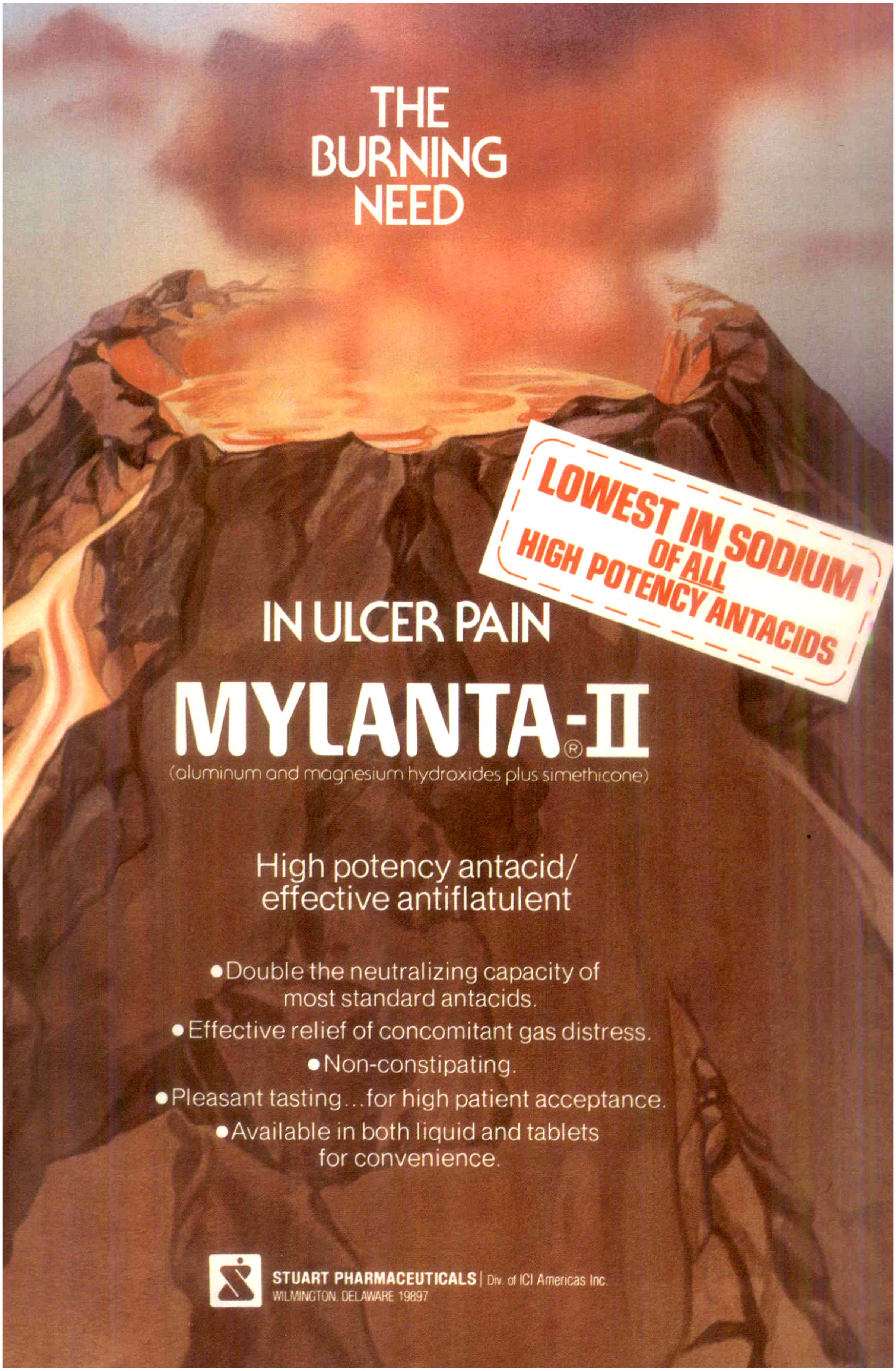

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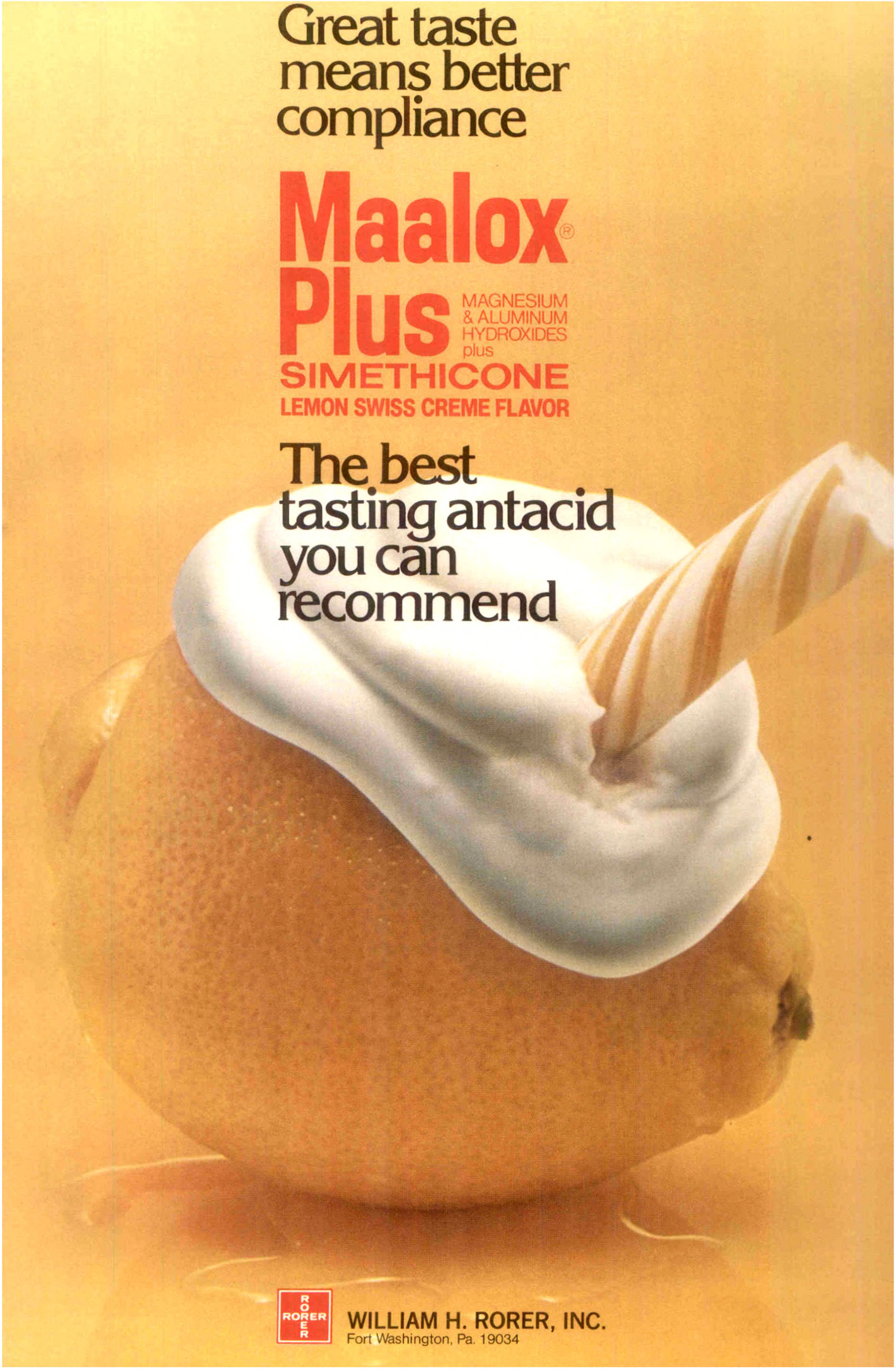

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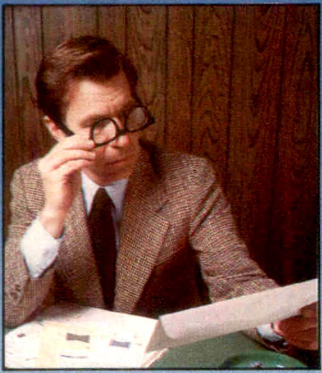
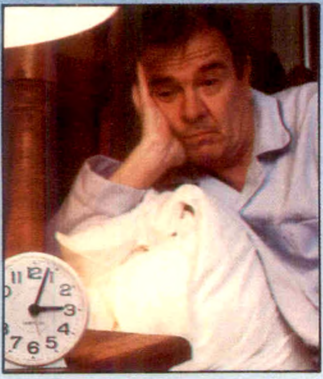
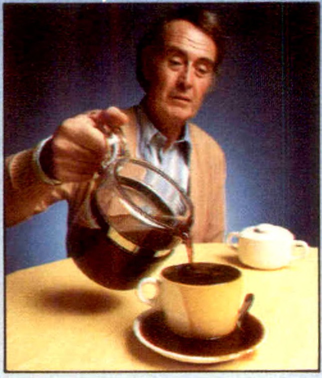
Which of these cirrhotic patients has portal-systemic encephalopathy (PSE)?

(Also called Hepatic Encephalopathy, Hepatic Coma.)







(Please turn page for answer.)

Cephulac®

(lactulose) Syrup

Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose diet.

WARNINGS: *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

7-3292(Y366A)

MEETINGS OF INTEREST

43rd Annual Convention, American College of Gastroenterology, The Marriott, Denver, Colo., 24-27 September 1978.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, The Marriott, Denver, Colo., 28-30 September 1978.

One Day of Gastroenterology, Postgraduate Course co-sponsored by the American College of Gastroenterology, the Southern Medical Association. Georgia World Congress Center, Atlanta, Ga., 11 November 1978.

They all do!

Case 1. 53-year-old retired submariner with cirrhosis of uncertain etiology and portacaval shunt

Case 2. 57-year-old widow with primary biliary cirrhosis

Case 3. 50-year-old male with alcoholic cirrhosis

Case 4. 43-year-old salesman with clinically stable Laennec's cirrhosis

Case 5. 55-year-old male with histologically proven cirrhosis

Case 6. 50-year-old male with Laennec's cirrhosis and portacaval shunt

Professional models were used to ensure patient privacy.

Suspect portal-systemic encephalopathy (PSE) in every patient with cirrhosis

Common early symptoms of PSE are:

irritability, euphoria, lack of concern for others, inappropriate behavior, faraway look, inversion of sleep pattern.

Results of recent investigations of PSE:

- Two-thirds of cirrhotic patients with portal hypertension without clinical evidence of PSE revealed impairment of cerebral function on psychometric testing. This dysfunction was in the same range as in patients with brain damage after blunt trauma[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment[3]

These inapparent and early stages can last for hours, days, weeks, months or even years. Untreated, they lead to COMA. You can't depend on routine observation to detect PSE.

- Test every cirrhotic for PSE.
- Treat every PSE, regardless of stage.
- Remember, the early stages are the most common; the coma stage is only the tip of the PSE iceberg.

Cephulac (lactulose) Syrup effectively reverses acute and chronic recurrent PSE in over 75% of episodes, without serious adverse reactions, when used as directed.

- lowers blood ammonia levels
- improves mental state
- lessens EEG abnormalities
- permits more normal dietary protein intake
- makes it easier to treat the patient

References:

1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.

2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non-cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.

3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: Detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 72:1119, 1977.

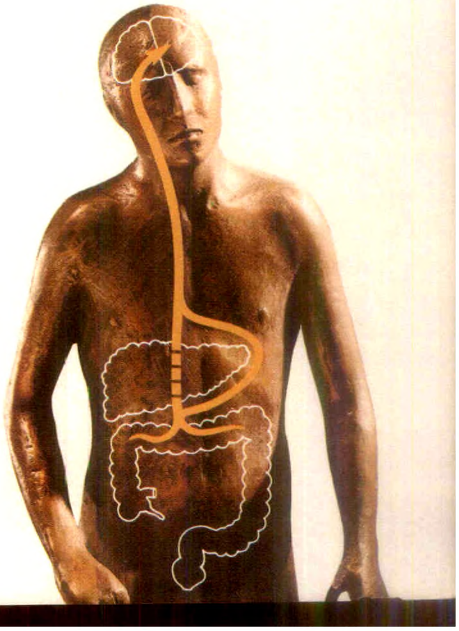
See adjacent page for prescribing information.

Cephulac®
(lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

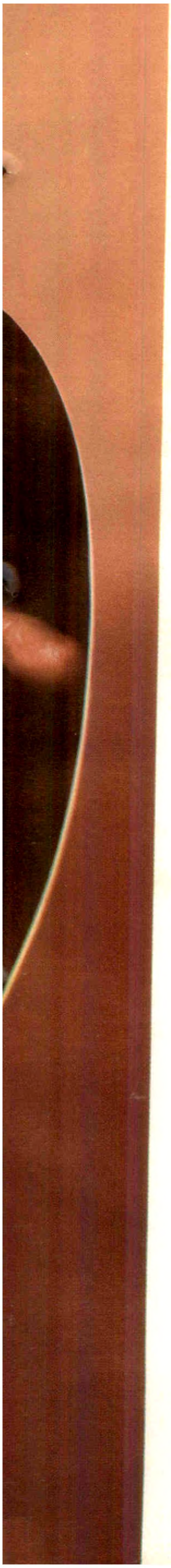
for the prevention and treatment of portal-systemic encephalopathy

(Also called Hepatic Encephalopathy, Hepatic Coma.)



The above advertisement will appear in:
American Journal of Digestive Diseases, American Journal of Gastroenterology,
Annals of Internal Medicine, New England Journal of Medicine in

Some anxious ulcer patients manage to avoid every irritant...
CAFFEINE
FOODS HIGH IN ACID
SMOKING



ROCHE

...except excessive anxiety

While his ulcer is still in its active stage, the patient is usually quite scrupulous about following "doctor's orders." For the time being, at least, he's willing to forego coffee, alcohol, spicy foods, even cigarettes. But there's one irritant that some of these anxious ulcer patients may be unable to avoid—or to handle. Excessive anxiety.

For such patients, specific antianxiety medication is frequently indicated in addition to counseling and reassurance—that is where Valium (diazepam) comes in. Valium is a useful, highly dependable calming agent that works promptly to relax the patient and relieve his psychic tension and anxiety. The characteristic response it produces is one that you know, want and trust.

Valium (diazepam) can particularly benefit the ulcer patient whose psychic tension increases at bedtime. The addition of an *h.s.* dose of Valium to a *b.i.d.* or *t.i.d.* regimen can reduce "nighttime" anxiety and thus may encourage sleep. At recommended dosages, Valium is usually well tolerated. Although drowsiness, ataxia and fatigue are sometimes encountered, these and more serious side effects are rarely a problem.

VALIUM® (diazepam) Ⓘⓥ

2-mg, 5-mg, 10-mg scored tablets

can relieve the ulcer patient's psychic tension and anxiety

Before prescribing, please see following page for a summary of product information.

VALIUM®
(diazepam)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

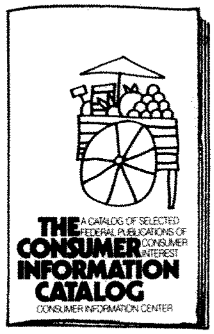
Supplied: Valium Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

"I CAN HELP CHANGE YOUR LIFE. BUT I CAN'T HELP CHANGE YOUR SPARK PLUGS."

If you want to find inner peace, come see me. But ask me how to fix a car? You got me. For questions of that nature, you must seek knowledge somewhere else.

A good place would be the Consumer Information Catalog. It is put out by the Federal Government and lists over 200 consumer booklets that one can send away for. Most are free. And they can help you in many areas that I cannot. From raising tomatoes to lowering your fuel costs.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A catalog of over 200 helpful publications.

GSA
General Services Administration • Consumer Information Center

Because every patient's needs are different, Fleet® provides a complete line of bowel evacuants.

C.B. Fleet Co. has served the medical profession for more than 100 years...a record built on the highest standards for product quality and satisfaction.

Maintaining this leadership position, Fleet® has developed additional products to meet the increasing needs of practitioners.

Now you have the most complete line of products suitable for any need, with any patient, in any situation where bowel evacuation is required.

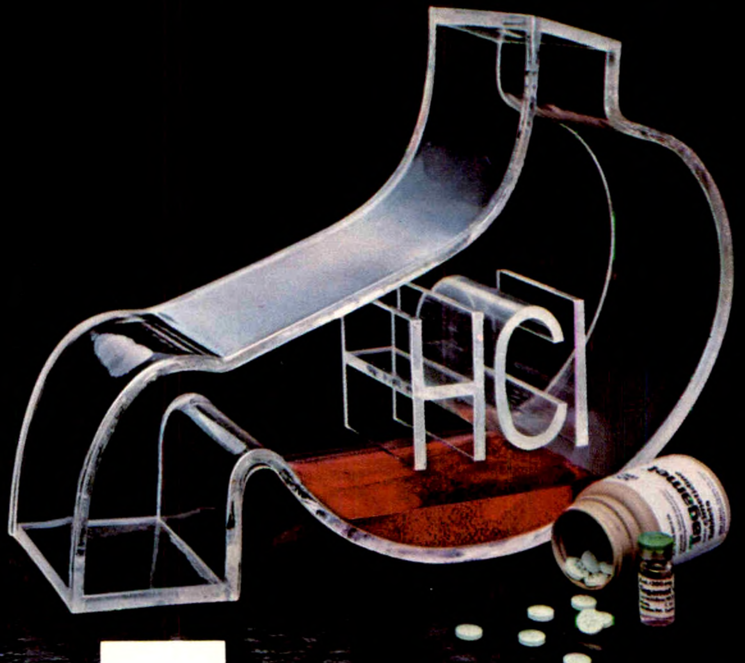
Fleet ready-to-use enema
For relief of constipation and bowel cleansing
Comfortip™
4½ Fluid Ounces (133 ml)
Fleet ready-to-use mineral oil enema
Stool softener and lubricant
Comfortip™
4½ Fluid Ounces (133 ml)
Fleet ready-to-use enema for children
For relief of constipation and bowel cleansing
Comfortip™
2¼ Fluid Ounces (66.6 ml)
Fleet Phospho-soda buffered saline laxative
For the relief of constipation
6 Fluid Ounces
Fleet Phospho-soda buffered saline laxative flavored
For the relief of constipation
2½ Fluid Ounces
Fleet Bisacodyl Laxative
Enteric Coated Tablets
twelve 100-tablet bottles
5 mg. each tablet
Fleet Bisacodyl Laxative
100 suppositories
10 mg. each
Fleet ready-to-use bisacodyl enema
10 mg. Rectal Contact Laxative
Comfortip
1¼ Fluid Ounces (37 ml)
NDC 0132-0211-01
Fleet Barium Enema Prep Kit
1
CONTENTS: FLEET® PHOSPHO-SODA BUFFERED SALINE LAXATIVE, 1½ FL. OZ. (45 ML); FLEET® BISACODYL, NF CONTACT LAXATIVE, 4 ENTERIC-COATED TABLETS, 5 MG EA.; FLEET® BISACODYL, NF CONTACT LAXATIVE, 1 SUPPOSITORY, 10 MG.
NDC 0132-0210-01
Fleet Barium Enema Prep Kit
2
CONTENTS: FLEET® PHOSPHO-SODA BUFFERED SALINE LAXATIVE, 1½ FL. OZ. (45 ML); FLEET® BISACODYL, NF CONTACT LAXATIVE, 4 ENTERIC-COATED TABLETS, 5 MG EA; FLEET® BAGENEMA, 1 UNIT; SOAPSUDS PACKET (1)
Fleet brand bagenema
FOR RELIEF OF CONSTIPATION AND BOWEL CLEANSING
Complete General Purpose LARGE VOLUME ENEMA SET (Disposable)
Fleet bagenema
NDC 0132-0212-01
Fleet Barium Enema Prep Kit
3
CONTENTS: FLEET® PHOSPHO-SODA BUFFERED SALINE LAXATIVE, 1½ FL. OZ. (45 ML); FLEET® BISACODYL, NF CONTACT LAXATIVE, 4 ENTERIC-COATED TABLETS, 5 MG EA.; FLEET® READY-TO-USE BISACODYL ENEMA, 10 MG BISACODYL, U.S.P.

When bowel evacuation is specified, Fleet® should be too.

Fleet brand pharmaceuticals

C.B. FLEET CO., INC.
Lynchburg, Va. 24505

Significant gastric acid suppression means effective duodenal ulcer therapy



Tagamet®

brand of cimetidine

Tablets, 300 mg. Injection, 300 mg./2 m

The H_2 Receptor Antagonist

Working directly at the parietal cell, 'Tagamet' suppresses gastric acid secretion after meals and throughout the night, producing important patient benefits:

- **rapid ulcer healing**
- **effective symptom relief, day and night**

In *Duodenal Ulcer,* the recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been demonstrated endoscopically.

In *Pathological Hypersecretory Disorders,* the dosage is also 300 mg. four times a day, with meals and at bedtime. In some patients it may be necessary to administer 'Tagamet' 300 mg. doses more frequently (not to exceed 2400 mg. per day) and continue as long as clinically indicated.

Dosage should be reduced in patients with impaired renal function.

Concomitant antacids should be given as needed for relief of pain.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of child-bearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of neutropenia have been reported, but no causal relationship could be established. Small, regularly observed, reversible increases in plasma creatinine and some increases in serum transaminase have been reported.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

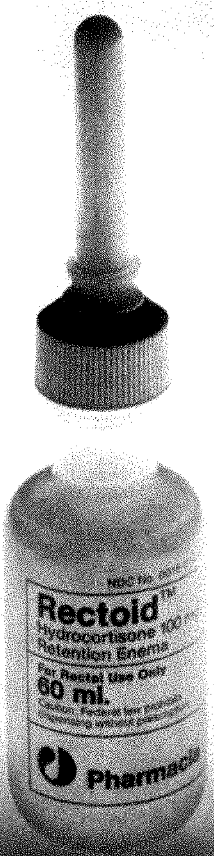
Injection: 300 mg./2 ml. in single-dose vials in packages of 10.

Date of issuance Sept. 1977

SK&F LAB CO., Carolina, P.R. 00630

Tagamet®
brand of
cimetidine

SK&F LAB CO.
a SmithKline company



RECTOID®

Hydrocortisone Retention Enema

☐ **Goes right to the site of the problem** to speed medication where it's needed most for prompt, direct relief
☐ **An effective alternative to oral corticosteroids**—lessens risk of possible complications due to systemic absorption
☐ **Provides soothing, direct relief** from ulcerative colitis symptoms—effective medication in a vehicle providing coverage of inflamed colonic mucosa
☐ **Premeasured, prefilled, prelubricated, disposable**—for unit-dose convenience, dosage accuracy, patient comfort
☐ **Supplied in a convenient, economical seven-pack**—designed to meet your prescribing needs
☐ **From the leaders in chemotherapy of ulcerative colitis for over 30 years.**

See facing page for brief summary of prescribing information.

New from Pharmacia

THE MOST DIRECT ROUTE TO RELIEF IN ULCERATIVE COLITIS

RECTOID®

Hydrocortisone Retention Enema

INDICATIONS: Adjunctive therapy in the treatment of ulcerative colitis.
CONTRAINDICATIONS: Systemic fungal infections; during the immediate or early postoperative period following ileocolostomy.
WARNINGS: Prolonged use may cause systemic reactions. Do not delay needed surgery while awaiting response to medical treatment. Proper insertion of the enema tip is essential to prevent rectal wall damage. Increased dosages are indicated before, during and after unusually stressful situations. Signs of infection may be masked, and new infections may appear, along with decreased resistance and decreased ability to localize infection.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Adequate human reproduction studies have not been done with corticosteroids. In pregnancy, nursing mothers or women of childbearing potential, weigh the possible benefits of the drug against the possible hazards to the mother and the embryo or fetus. Observe infants born of mothers treated during pregnancy for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention and increased excretion of potassium, requiring dietary restrictions and supplementation, may occur. All corticosteroids increase calcium excretion. *Immunization procedures, especially against smallpox, should not be undertaken in patients receiving corticosteroids, because of the possible hazard of neurological complications and lack of antibody response.* Close observation and chemoprophylaxis are indicated in patients with latent tuberculosis or tuberculin reactivity.
PRECAUTIONS: Use with caution in cases of impending perforation, abscess or other pyogenic infection, fresh intestinal anastomoses, obstruction, extensive fistulas, and in the presence of active or latent peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis, or myasthenia gravis. Surgical prognosis may be impaired by increased infection hazard. Administer larger dose of appropriate antibiotics if infection is suspected. Drug-induced secondary adrenocortical insufficiency, minimized by a gradual dosage reduction, may occur with prolonged therapy. This condition may persist for months after discontinuation of therapy; therefore, hormone therapy should be reinstituted during periods of stress. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Corticosteroids exhibit an enhanced effect in patients with hypothyroidism and cirrhosis and should be used cautiously in patients with ocular herpes simplex because of possible cornea perforation. Use the lowest possible dose to control the condition and institute a gradual dosage reduction as soon as possible.

Psychic derangement may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.
ADVERSE REACTIONS: Local pain or burning, rectal bleeding, and apparent exacerbations of the disease or sensitivity reactions may occur in rare instances. The following adverse reactions should be kept in mind whenever corticosteroids are given.
Fluid and Electrolyte Disturbances. Sodium retention; fluid retention, congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal.* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage, pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin, petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurological:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities, development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirement for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: The usual course of therapy is one RECTOID enema nightly for 21 days.

Sigmoidoscopic examination and x-ray visualization are essential for adequate monitoring.
HOW SUPPLIED: Boxes of seven 60 ml (hydrocortisone 100 mg) disposable single dose bottles with lubricated rectal applicator tips.
IMPORTANT: See full prescribing information before administering RECTOID.

Pharmacia

Pharmacia Laboratories
Division of Pharmacia Inc.
Piscataway, New Jersey 08854

NEW CATALOG.

Quinton's new catalog of gastrointestinal biopsy instruments, including the Multipurpose, Peroral Hydraulic and Crosby-Kugler instruments, is now available. For your free copy call toll free: 1-800-426-0538, or contact Quinton Instrument Co., Dept. B-17, 2121 Terry Avenue, Seattle, WA 98121 (206/223-7373).

QUINTON

Now ... the AMA brings CME to you!

As you're aware, state medical societies, specialty societies, and other medical groups in increasing numbers are making continuing medical education (CME) a requirement for membership. Already some state licensure boards are requiring CME for relicensure.

Recognizing its importance to members, the AMA has greatly expanded its CME programming. In 1977, your AMA will offer 15 regional meetings, as well as scientific programs at the Annual convention and Winter Meeting.

These new regional meetings make it easier, more convenient for you to fulfill your CME needs by bringing the programs closer to your hometown and scheduling them on weekends to avoid interference with your practice.

All courses are approved by the AMA Council on Continuing Medical Education as meeting the criteria for Category 1 toward the AMA Physician's Recognition Award, which certifies completion of 150 hours of CME over three years. Since the initiation of the PRA program in 1969, more than 58,000 physicians have qualified and/or requalified for the award.

CME is just one of the many vital services the AMA provides for its members. With your support, it can do even more.

CME

Join us.
We can do much more together.

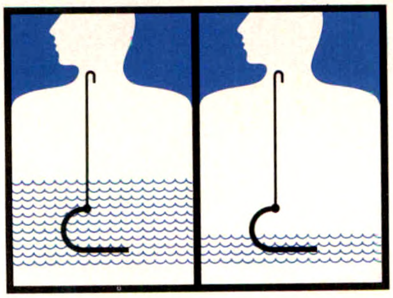
Dept. of Membership Development
American Medical Association
535 N. Dearborn St./Chicago, IL 60610

Please send me more information on the AMA and AMA membership.

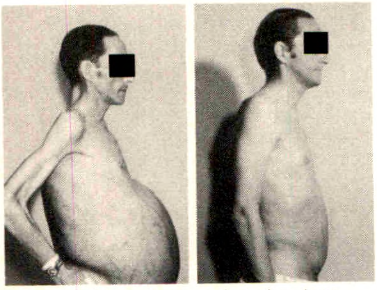
Name ______________________

Address ______________________

City/State/Zip ______________________



The LEVEEN Peritoneo-Venous Shunt.
A device that can contribute significantly to the medical treatment of refractory ascites.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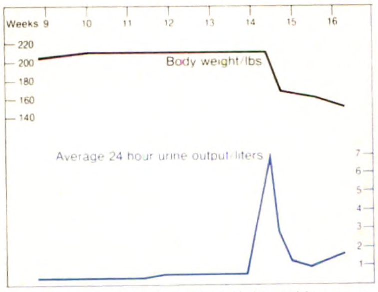
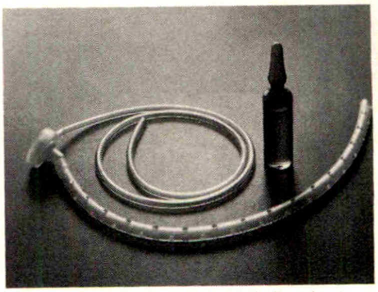
Typical girth reduction in patient after shunt installation.



Note dramatic drop in body weight and increase in urine output.



The shunt acts in conjunction *with* diuretics to increase patient comfort and mobility.

Refractory ascites has traditionally been a medically-managed problem, often complicated by increased aldosterone, creatinine and BUN levels, reduced sodium clearance, and progressively increasing oliguria. The treatment of choice, which usually includes a salt-restricted diet and a regimen of powerful diuretics, eventually may only mobilize the ascitic fluid at the expense of renal function. The patient often requires repeated hospitalization as fluid becomes more and more difficult to mobilize, and increased girth, breathing difficulty, nutritional deficiency and renal complications reduce the patient's mobility, comfort and longevity.

Not a cure or a solution by itself, but, combined with diuretic treatment, a promising improvement in patient comfort and longevity[2].
Easily implanted, the LEVEEN Peritoneo-Venous Shunt offers another tool to simplify this usually difficult course of patient management. By means of a pressure-activated valve with attached tubing, the shunt routes fluid from the peritonel cavity into the superior vena cava. Thus by increasing the intravascular fluid, the shunt may help to prevent or actually reverse the hepato-renal syndrome[6], while it can allow a wider safety margin for the use of diuretics without causing kidney damage.

Urine output increased, girth reduced.
Studies have shown that patients with the shunt implanted usually present a drop in aldosterone, creatinine, and BUN levels, with increased sodium clearance, urine output, and reduced girth and body weight. All of these results usually occur within 24 hours after shunt installation.[1-8] In one 1977 study of 28 patients, mean urine flow increased from 607 ml to 4,254 ml, mean abdominal girth dropped from 108 to 93 cm, mean BUN level fell from 39 to 23 mg/100 ml, and the mean plasma creatinine level was reduced from 2.4 to 1.8 mg/100 ml[4].

More mobility, less hospitalization.
In the same 1977 study, most patients were discharged within 10 to 15 days after surgery, and after 18 months, nearly half were still alive. Of patients who had a bilirubin value of less than 10 mg/100 ml and no signs of severe encephalopathy or recent GI bleeding, 71% were alive after 18 months.[4] Even after shunt implantation, patients still require medical attention, but will not, in most cases, remain hospital-bound, and will require less of the physician's time. Increased patient comfort and reduced hospital dependency will restore some degree of mobility and normality to the ascitic patient.

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Indications For Use:
The LeVeen Peritoneo-Venous Shunt may be indicated when the patient does not respond promptly to intensive medical management.

The shunt is designed to eliminate the accumulation of ascitic fluid. Shunt placement should be considered for treatment of ascites complicating the following conditions:

1. Cirrhosis
2. Budd-Chiari Syndrome
3. Chylous Ascites
4. Nephrogenic Ascites
5. Biliary Atresia
6. Amyloidosis
7. Cryptogenic Ascites

Contraindications For Use:
In certain patients, the LeVeen Peritoneo-Venous Shunt will not be effective, or may be contraindicated because of secondary complications that outweigh its benefits. These conditions are:

1. **Peritonitis.** This should always be suspected when the peritoneal fluid is turbid. Peritonitis can occur without the usual signs and symptoms in patients with ascites.
2. **Esophageal Varices.** With A Recent History Of Bleeding. If ascites and variceal bleeding are present concurrently, treating the varices first may be indicated.
3. **Renal Failure.** The shunt will not reverse the renal damage in patients with acute tubular necrosis or other types of primary renal failure. A low urine sodium concentration may be the best indication that the tubules are functional and may respond to a shunt.
4. **Bilirubin level above 10 mg/dl**

Cautions:

1. **Esophageal Varices.** Without Recent Bleeding. In patients whose varices have been treated surgically, the shunt may be effective.
2. **Neoplastic Ascites.** The LeVeen Peritoneo-Venous Shunt has been used with success in patients with intractable ascites associated with primary or metastatic intra-abdominal neoplasms.[3] The use of the shunt in such patients requires weighing the shunt's potential benefits against the possible hazard of generalized dissemination of neoplastic cells which are commonly present in the ascitic fluid of these patients.
3. **Associated Cardiac Disease.** Cardiac patients may be sensitive to increased blood volume due to sudden recirculation of large quantities of ascitic fluid. Removal of accumulated ascitic fluid from the abdomen at the time of shunt placement may be indicated in such patients.

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Recent Advances in Gastrointestinal Endoscopy

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Since 1970 considerable advances have been made in the field of fiberoptical endoscopy. One essential factor is that a greater variety and more efficient instruments became available. The development moved first in the direction of a more precise diagnosis and second in the direction of therapeutic or operative endoscopy.

ADVANCES IN DIAGNOSIS

Emergency endoscopy:—Within a few years, it has become possible by using fiberoptics, to inspect the upper gastrointestinal tract and the colon, including the terminal ileum, as well as with certain limitations, the small intestine lying in between. The latter problem is not yet sufficiently solved. It followed from this that in the case of acute bleeding, it is not necessary to wait until the bleeding has stopped but it is possible to apply endoscopy immediately and after drawing away the accumulation of blood, to establish the seat of the bleeding.

The further therapeutic procedures would be dependent on the findings. This advancement simplifies matters considerably for the surgeon. False or incomplete diagnoses are avoided.

According to the statistics available, in almost 50% of patients with esophageal varices, bleeding is due to other lesions, for example gastric ulcers. In 10-30% of patients there are multiple lesions in the upper gastrointestinal tract, all of which are possible sources of bleeding. Radiology alone cannot solve the problem as to which is the actual source but may be aided by the use of angiography.[1]

Emergency endoscopy must answer the following questions: 1. Is active bleeding still present or has it stopped spontaneously? 2. Can the bleeding be treated conservatively e.g. by (laser) coagulation, or is an operation necessary? 3. Is an emergency operation necessary? 4. Must the operation to stop the blood flow be transthoracic or transabdominal?

The case history of the patient can lead to errors, especially where ulceration or other sources of bleeding have been found. More than a few patients have undergone operations as a result of a false

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The Joseph Abrams Memorial Lecture, presented at the New York Society for Gastrointestinal Endoscopy, New York, N. Y., 12 January 1977.

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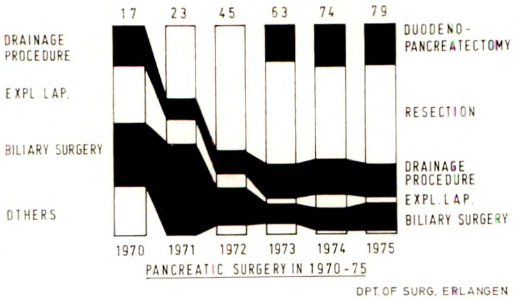

Fig. 1—Pancreatic surgery and ERCP.[5]

indication due to an improper or incomplete diagnosis, where final conclusions have been drawn too quickly.

Is the diagnostic luxury of having a round the clock emergency endoscopic service available worthwhile? In a computer analysis of 630 patients with acute gastric hemorrhage, made in 1974, Himal[2] obtained a mortality rate of 32% in the case of bleeding where the source was uncertain, as opposed to 9.5% where the source was known. Allan and Dykes[3] had to alter fundamentally their therapeutic procedure in 18% of their patients with bleeding, as a result of endoscopic findings.

The first prospective studies show clearly that by the use of emergency endoscopy the number of blood transfusions needed, the time required before operative intervention and the length of hospitalization can be significantly reduced. Further, Hellers and Ihre[4] are able to provide documentary evidence of a significant improvement in the prognosis of acute gastric hemorrhage. This clearly indicates the value of a diagnostic method.

The most effective region of application for emergency endoscopy is the upper gastrointestinal tract. The need for prior cleansing makes quick procedures in the colon difficult.

Those colleagues, who maintain that the therapeutic consequences of a correctly confirmed diagnosis provided, for example, by emergency endoscopy, would bring no advantage to the patient, would seem to have lapsed into this kind of spiritual arrogance and abstinence represented by Ivan Illich, that preacher of penance. Also, a too emphatically displayed self-limitation is a form of conceit.

ERCP:—Diagnostically, new ground was broken about seven years ago with the retrograde presentation of the biliary and pancreatic systems via the papilla of Vater. We have been utilizing this procedure since 1970. The type of pancreatic surgery has changed under the influence of ERCP[5] (Fig. 1). Since then ERCP has spread throughout the whole world and is well known. For this reason, only a few words are devoted to this aspect. Because of possible complications such as pancreatitis and cholangitis, the indications are more stringent. In the Medical University Clinic Erlangen, ERCP stands at the end of the diagnostic measures. By its use, confirmation is made whether a cholestasis can be relieved by an operative intervention or not. Where there are severe pains in the epigastric region, it can be used to decide whether an operation on the pancreas will effect a remedy. In other words, ERCP aids in the preoperative diagnosis and the exclusion of tumors.

There again, it would not be used, when with all probability an irritable colon is the cause of tolerable discomfort.

We have recognized, in view of cases of cholangitis and pancreatitis following ERCP, that the inner surface of the instruments can be supersaturated with pathogenic germs: *Pseudomonas aeruginosa, B. proteus, E. coli, Klebsiella,* S. *marescens, Str. faecalis* and *Candida*-types.

The instruments are more thoroughly disinfected than before and precautionary antibiotics, generally tetracyclin and gent-

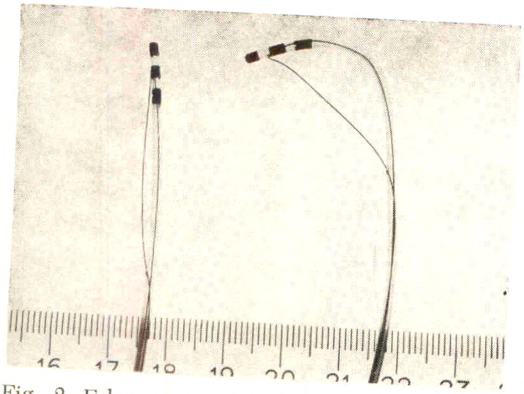

Fig. 2–Erlangen papillotom, in straight and bent position.

amycin are administered. Almost all of the above mentioned germs have proved themselves to be sensitive to these antibiotics.

Since then complications in the form of mild pancreatitis have arisen in only 0.9% of 400 cases. Recently we were shown a newly developed gastroduodenoscope made by Machida, in which the valves can be easily removed and disinfected. We regard this to be an important advance.

Contrast media containing disinfectant are in the course of development in our department of microbiology. By this means, germs normally present in the intestines, which have been transposed in the ductal systems, can be destroyed. Not only can endoscopy of the upper intestinal tract be used in conjunction with x-ray procedures, as is the case with ERCP but by the use of recently developed transgastroscopic ultrasonography,[6] the ultrasound (A-scan) is applied from the inside of the stomach outwards for diagnostic purposes.

Peroral cholangioscopy:—Until now cholangioscopy could only be performed intraoperatively. A new generation of endoscopes has been born. The latest member of the endoscope family is the babyscope with the motherscope (Olympus). A long side-viewing duodenoscope is used for the location of the papilla of Vater. Rinsing facilities allow a good view withi the ductal system. Since the babyscope mechanical quality and resistance of th fiber bundle is relatively poor, we hav until now used this procedure only in patients following endoscopic papillotomy Peroral cholangioscopy was performed o nine patients. The indication for this procedure was to look for retained concrement and in one patient to inspect a choledocha tumor. Because of its small diameter a biopsy is not possible using the babyscope. But under certain conditions it could be possible to obtain material from suspect tissue for cytological examination. In three patients concrements were still present which could be localized. One tumor formation, documented on the retrograde cholangiogram, proved to be a suture granuloma following cholecystectomy. Although the clinical indication seems to be rather limited, peroral cholangioscopy opens a new field in fiberendoscopy namely, inspection of small hollow organs in the human body. For pancreaticoscopy, problems in disinfection and avoiding vulneration of the pancreatic duct still have to be solved.

The new possibilities of peroral cholangioscopy still have to be evaluated in clinical practice.

Snare biopsy:—The introduction of snare biopsy represents an advance in the morphologically based diagnosis of gastric diseases.[7] It is superior to the conventional forceps biopsy.

An important disadvantage, which cannot be overcome, when using forceps for biopsy is that the particles only reach the *muscularis mucosae,* in those cases where the mucous membrane is normal or atrophic. If the mucous membrane is thickened, for example due to glandular (Zollinger-Ellison syndrome) or foveolar hyperplasia (Ménétrier's disease), then the diagnosis can only be made indirectly by

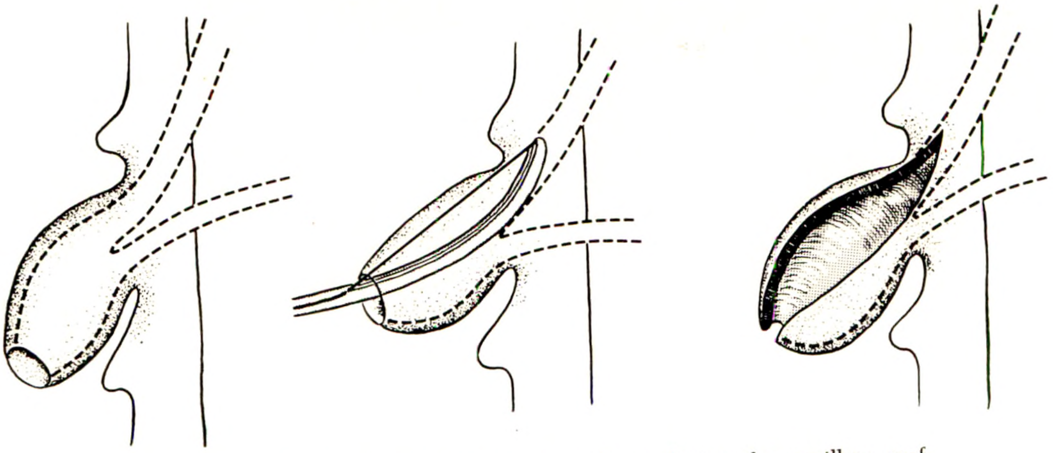

Fig. 3— Inserted papillotom, bent position, after splitting the papillary roof.

the fact that the *muscularis mucosae* is not contained in the approximately 1 mm. thick layer of tissue. Normally the submucous membrane remains out of reach. In this situation snare biopsy represents an advancement. Here a diathermic snare is laid over a thick or tumerous fold, such as a lasso and drawn together at the base of the formation. By tightening and withdrawing the snare, a polyp-like portion of tissue is constricted and lifted away from the rest of the wall. This formation can then be removed by electrocoagulation as in polypectomy. Snare biopsy reaches a depth of about 4 mm. in the case of thickened folds and up to 8 mm. deep where carcinomatous lesions are suspected.

Quantitively, a particle removed by snare biopsy corresponds to about 80 biopsy pieces removed in the conventional way with forceps. The most important diagnoses achieved with the help of snare biopsy are: Zollinger-Ellison syndrome; Ménétrier's disease, submucosal processes; lymphomas and carcinomas.

The question as to whether an extension of the diagnostic possibilities is obtained when additional tissue is taken with the forceps from the site of the ulcer, which results after taking a biopsy with the snare, must still be clarified. The information obtained from this "button-hole biopsy" appears to be impaired by the thermal lesion caused by electrocoagulation. In addition to its diagnostic value, the snare biopsy also has some significance in palliative therapy by electroresection of inoperable gastrointestinal tumors. In patients with stenosing carcinoma of the esophagus or of the cardia in whom no other measures were possible, a temporary improvement of the odynophagia or dysphagia was achieved. The main complication of snare biopsy is hemorrhage, 1-2%, mostly manageable by conservative means.

Operative endoscopy:—This is the logical consequence of the fact that a series of pathological changes in the gastrointestinal tract have become directly visible and thus, as it were, become more readily accessible. Endoscopists are therefore known to be more inclined to action than contemplation.[8] The first possibility and in the meantime, quantitatively the most important operation was polypectomy.

Polypectomy:—In the upper and lower gastrointestinal tract, it is relatively easy to carry out, if the polyp has reached a diameter of about 5 mm. and has not exceeded a diameter of 25 mm. It will be readily understood that types with stalks can be removed more easily than those having broader bases. Major operative intervention, because of relatively small lesions, can in this way be avoided in future.

Polypectomy as pure biopsy is diagnostic in character but it is also therapeutic if the malignant infiltration has not reached the basis of the polyp stalk, i.e. the point of polypectomy.

The "focal carcinoma" as a constituent of an adenomatous polyp is found on the colon in 5.8% of our material (410 cases).

With the aid of endoscopy, it is much easier than before to recognize polyps in the upper gastrointestinal tract and especially in the colon. By this means an astonishing number of polyps have been found; much more than previously. One has the impression that, if a person is found to have one polyp, then more probably exist or he will one day develop more. For this reason one is inclined to speak of a polyp disease. This disease is all the more significant, because of its close relationship to carcinoma, i.e. cancer in the colon frequently arises from polyps.

With the aid of endoscopic polypectomy, one will have in the forseeable future, a better over all picture of the problem. The following points are of interest, since they contribute to early diagnosis and thus can save human lives. 1. What types of polyps are there in the upper gastrointestinal tract? How high is the degeneration quota? 2. What types of polyps are there in the lower gastrointestinal tract? How high is the degeneration quota? 3. Is the polyp an indicator of the danger of carcinoma in the surrounding mucous membrane? 4. Is a polyp in the rectum an indicator of further polyps in the higher sections of the colon? 5. Is a polyp in the bowel an indicator of polyps in the stomach and vice versa?

Endoscopic papillotomy (EPT):—EPT signifies the most astonishing advance in operative endoscopy. In many cases, with its help a grave operative intervention can be avoided. We have utilized EPT for four years.[9] A report on our experience has already been given by my co-worker Koch in May, 1975 in San Antonio.[10]

Choledochal stones without, or more often with preceding cholecystectomy are no rarity. They always constitute an indication towards operative intervention, since they impede the outflow of gall. Cholestasis or cholangitis are, as a rule, the consequence. A severe pancreatitis also is always imminent.

Transduodenal sphincterotomy is truly an effective but, however, a major surgical operation. Since the endoscopist not only finds the papilla easily (apparently more easily than the surgeon) but also, as a rule, can intubate it well for diagnostic purposes, there arose the idea of carrying out the splitting of the papilla by endoscopic means, i.e. without opening the abdominal wall and the duodenum. The method has, in fact, proved practicable for us and has been used in Erlangen since 1973.[11]

INSTRUMENTS

For endoscopic papillotomy, the Olympus duodenoscope JFB 2 is used in conjunction with a high frequency diathermic probe developed by us[12, 13] (Fig. 2). As opposed to Sohma's papillotom, used by Japanese colleagues, it has proved itself very well.

TECHNIC

The duodenoscope is inserted with the patient lying on his left side. As soon as the instrument has reached the papilla the patient turns onto his stomach. Subsequently there follows the cannulation of the papilla of Vater. By administering contrast

TABLE I

INDICATIONS FOR ENDOSCOPIC PAPILLOTOMY

1. Choledochus concrements with risk patients*	92
2. Choledochus concrements following cholecystectomy (non risk patients)	78
3. Papilla stenosis without concrements	16
4. Gallbladder and choledochus concrements (in combination with papilla stenosis)	7
	193
Unsuccessful	8
Total	185

* With and without cholecystectomy

medium (Conray 60®), the biliary system can be seen, using x-rays. A radiograph is made. Following this the pressure in the biliary system can be measured by means of a Statham element (DB 23). The catheter is finally removed—the biliary system is still sufficiently filled with contrast medium —and in its place the papillotom in the straight condition is inserted as far into the choledochus so that the emergence of the steel wire from the lower part of the catheter's tip can still just be visualized via the endoscope. At this point, the tip of the probe is flexed. If the positioning is good, the papilla dome will rise up from its base and ride on the steel wire perpendicular to the intestinal lumen (Fig. 3). But the endoscopic aspect alone is insufficient for positive differentiation, whether the probe is lying in the choledochus or in the pancreatic duct. An additional radiographic check is necessary. The papillotomy can then be done. As in surgical splitting, the sphincter papillas as well as the choledochal sphincter are divided. As a rule, the choledochus opens with a jerk and allows its dark, mainly gall-filled lumen to be seen. In adequate sphincterotomy, the length of the cut measures between 15 and 25 mm. After papillotomy the stone either falls out of its own accord or remains in the choledochus. Depending on the urgency of stone removal, it is possible to wait until the concrement passes of its own accord, or to follow at once with an extraction attempt using a Dormia basket. Because the manipulation in the biliary system can produce lesions in the wall epithelium and because there is the danger that a bacteremia can be caused and furthermore, because larger stones sometimes become jammed during an extraction attempt, we are inclined to await a spontaneous ejection of the stone during the course of the following week. The patients are encouraged to examine their stools for concrements.

INDICATIONS

An obvious indication for endoscopic papillotomy with the object of removing concrements from the choledochus are patients having previously had cholecystectomy, who thus have increased operation risk. If indeed the general condition of the patient is so poor that an operation, necessitated by complications, would in all probability lead to death, then papillotomy should not be attempted. An exception here is the situation where this operation offers the last chance, when performed, for example, to terminate cholangitis, which in a short time would lead to a fatal outcome.

Choledochal stones following a preceding cholecystectomy in patients also without an increased operation risk and when they suffer from recurring colic and symptoms of cholestasis, constitute a more extended indication.

Papillotomy can also be carried out successfully in cases of effective distal papillary stenosis.

The most extensive indication for papillotomy would exist in those patients,

TABLE II

STONE REMOVAL FOLLOWING ENDOSCOPIC PAPILLOTOMY

1. Spontaneous		94
2. Extraction with Dormia-basket		62
a) directly following EPT	36	
b) 3-7 days following EPT	26	
3. Negative		11
4. No follow-up		2
Total		169

where the stone filled gallbladder is still *in situ*. The object of papillotomy and removal of stones from the choledochus is to spare the patient a surgical opening of the duct and/or the duodenum. The first step is papillotomy with stone removal by means of the endoscope; the second step is cholecystectomy.

CONTRAINDICATIONS

Endoscopic papillotomy is contraindicated where there is tendency to bleeding.

A further contraindication exists, when the size of the concrement makes it appear improbable that papillotomy would result in the removal of the stone. Particularly unfavorable is the case, where the choledochus lumen narrows down towards the papilla in the form of a carrot.

RESULTS

Until October, 1976 papillotomy had been attempted with 193 patients at the Medical University Clinic Erlangen. Among these were 92 risk patients, 78 nonrisk patients, 16 patients with papillary stenosis without concrements and seven cases, where there were both gallbladder and choledochal concrements in combination with papillary stenosis. In eight of these cases, using the papillotom was not successful (Table I).

TABLE III

COMPLICATIONS FOLLOWING ENDOSCOPIC PAPILLOTOMY

	No.	%
Pancreatitis	7[*]	3.8
Pancreatitis plus bleeding	1[†]	1.6
Bleeding	2[‡]	
Perforation	1[**]	
Purulent cholangitis	(+) 1	
Total		6.5
Fatalities		0.54

[*] Of these 2 severe, no operation
[†] Operation necessary
[‡] An additional operation was necessary
[**] Conservatively controlled

Endoscopic papillotomy was successfully carried out in 185 patients. Ninety-four times the concrements came out spontaneously, 62 times they were extracted by the use of the Dormia basket; 11 times, a success could not be indicated and two patients did not wish to undergo the check (Table II).

The breaking of the gallstones in the choledochus by means of spark discharge and shock waves has already shown itself, in our department, as being applicable, in principle, to human beings. We hope soon to achieve the breaking up of stones in the gall passages, by the use of ultrasonics.

COMPLICATIONS

In our experience pancreatitis is the most important complication. It occurred in 3.8% of the cases. In 1.1% it was severe but healed under conservative treatment. The next most frequent complication is bleeding at 1.6%. A perforation proved amenable to conservative treatment. In a patient with a past history of cholangitis, this was reactivated by the attempt to extract a stone. A septic shock occurred which, however, could be controlled by appropriate measures and operative intervention. The woman patient died, however, 12 days after the surgical operation from a liver failure. The mortality rate of papillotomy among our patients up to now equals to 0.54% (Table III).

Up to this time the mortality rate of all 880 endoscopic papillotomies performed in Germany is 1.7%; if the three cases not performed with the Erlangen papillotom are subtracted, the mortality rate is 1.25%; the complication rate amounting to 7.3%.

ENDOSCOPIC PAPPILLOTOMY VERSUS SURGICAL PAPILLOTOMY

For a number of patients, endoscopic papillotomy affords a new possibility of removing concrements from the choledochus. According to statistics collected by Hess[14] the mortality rate of surgical transduodenal sphincterotomy is 7.6%. For endoscopic papillotomy, it is between 1% and 2%.

An essential complication avoided by endoscopic papillotomy, is the insufficiency of the duodenal suture. Lesions of the pancreatic tissue and pancreatic duct with consecutive pancreatitis occur not only with surgical but also with endoscopic procedures. With surgical papillotomy the occurrence of pancreatitis is on the average estimated at 4% (Schwemmle, personal communication). In our patients, it is at about 4.6%. It was so severe, however, in only 1.3% of cases as to cause concern. Perforation of the rear duodenal wall can occur with surgical, as well as with endoscopic procedures. With the latter method, however, it occurs extraordinarily rarely. In addition to this, the endoscopic method has the advantage that the escape of contrast medium would show up radiologically and this complication would be immediately recognized. As a rule conservative treatment is adequate. Also, bleeding can be recognized endoscopically and can be controlled conservatively, or, if necessary, by an operation. Special care is needed, when a concrement jams as a consequence of an attempt at extraction. Increase in temperature and the circulatory condition must be carefully checked. If there is a suspicion of reactivated cholangitis, then surgical stone removal should be undertaken without hesitation.

The question of the repetition of stenosis arises in the case of endoscopic papillotomy as well as in surgical splitting without suture. We did not encounter it to any noticeable degree. Follow-up examinations, one year after endoscopic papillotomy, have been carried out in 36 patients. No real restenosing of the papilla, nor clinical or chemical signs of cholangitis have been found.

STOPPING HEMORRHAGE BY ENDOSCOPIC MEANS

Bleeding in the gastrointestinal tract can occur because of ulceration, deformation of blood vessels or from places where polyps have been removed. Until recently the endoscopist was limited in diagnosis. The feeling of helplessness led him to consider ways and means whereby the endoscope could be applied therapeutically. Truly the problem is not finally solved but shows hopeful beginnings. Electrocoagulation is used. It is, however, attended by a not altogether small risk of perforation, if the application is to be effective. The coagulating instrument dips into a pool of blood, whose depth is difficult to estimate. In this situation it seems better to use laser light, which promises a more readily visible and regulatable application.

LASER PHOTOCOAGULATION

In contrast to normal light, laser waves are coherent, that is parallel light at a single wavelength (monochromatic). By focusing, this light can be concentrated on a very small region with high power densities. Absorption of laser light by the tissue surface causes conversion of light into thermal energy. Fruehmorgen performed systematic experimental studies mainly with the argon-ion laser.[15] Clinical experience is already achieved.[16] The emission of the argon-laser in the green-blue range leads to a maximum absorption and thus an optimal effect in red tissue areas.

Experimental studies showed the following results: 1. The beam of the argon-ion laser produces tissue reaction (edema, coagulation, charring) in the gastrointestinal tract. 2. The location of maximum reaction (coagulation) in the therapeutic range is the submucosa.

This effect is at least partly due to the maximum absorption in the red tissue areas. In consequence charring of tissue causes a self-limitation of absorbed energy, because the color changes from red to black. The coagulation of blood vessels was dependent on their diameter. Artificial bleeding could be controlled from veins up to a diameter of 2 mm. and from arteries up to a diameter of 1 mm. By the development of a new flexible plastic fiber as a transmission system the laser became feasible for fiberendoscopes. The following factors speak in favor of laser coagulation: 1. no tissue contact; 2. control under endoscopic vision; 3. no flow of current through body tissue; 4. broader therapeutic range; 5. selective absorption; 6. autoinhibition of penetration.

At the present time two different qualities of laser light are competing, the Argon-ion and the Neodym YAG laser. They have different effects, which depend upon the different spectral absorption properties of the tissue. Argon laser light is absorbed selectively by the blood and thus by the blood vessels.

This does not apply to the Neodym YAG laser beam. The absorption of the YAG laser output by the blood and by tissues perfused by blood is about four to five times less than is the case with the Argon laser. Thus, to stop bleeding, four to five times the quantity of YAG laser light is required per unit of time, than with the Argon laser beam.

This means that when using the Neodym YAG laser, large quantities of heat energy penetrate the tissues unnecessarily and there bring about changes, which in some circumstances give rise to perforation of the hollow organ. With the Argon laser an adequate effect on the blood vessels of the submucosa in the therapeutic region is achieved.

In clinical application of the Argon Laser at Erlangen, it has been possible to coagulate 94 bleeding lesions or potential sources of bleeding as for example telangiectasias, without complications.

On the basis of our experimental and clinical observations up to the present time,[17] the following conclusions can be drawn: 1. All therapeutic effects, which can be achieved by the YAG beam, can be achieved by the Argon laser. 2. The risk of perforation with the YAG laser is larger as opposed to that of the Argon laser and this risk applies also in the therapeutic region.

At the present time the Argon laser is therefore preferred to the YAG laser in clinical application.

With our coagulator, a CO_2 gas jet, emerging parallel to the laser light, blows the blood to the side, so that the source of bleeding itself is revealed and can be better coagulated. We believe this to be a further important advantage of our Argon-ion coagulator.

Impressive progress in fiberoptic endoscopy has been achieved. With the introduction of glass fiberoptics, gastrointestinal endoscopy became a procedure with almost no risks. New and serious problems arose within the framework of ERCP. It has become essential to deal emphatically with the problem of eliminating bacteria and it is desirable that the industry should be more active in this sector than previously. Suitable equipment for disinfecting the endoscope is just as necessary as material for the endoscope itself, which will stand up to disinfecting and new designs which will simplify cleansing. Almost certainly the most important advance in the field of modern gastrointestinal endoscopy is the application for therapeutical purposes.[18]

Operative endoscopy reduces the risks as opposed to classical surgery but by the nature of things, it cannot remain completely without complications. On this point physician, patient and, last but not least, legal responsibility must be clear. So far as legal responsibility is concerned, especially in the United States and also in West Germany, there has been an unfavorable turn. One forgets or likes to forget that every human action has imperfections, from which medical procedures are not exempt. It will depend partly on the insight of jurisdiction, whether development in medicine can go further. Trials for witchcraft have brought no progress to humanity but without doubt progress has been brought about by the endeavors and the errors of those who have broken new ground.

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The Lower Esophageal Ring and Esophageal Reflux

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Although the lower esophageal ring is an important cause of dysphagia in adults, its pathogenesis is unknown. To better define the relationship between the lower esophageal ring and esophageal reflux, we analyzed, retrospectively, the records of 18 hospitalized patients with radiologically demonstrated rings (16 confirmed by endoscopy and/or surgery). In 16 of these patients, evidence of esophageal reflux including at least one of the following was present: overt esophagitis noted at endoscopy or surgery (14 cases), histologic evidence of esophagitis (3 cases), and/or symptoms of pyrosis or free reflux (13 cases). These findings suggest that 1. reflux is frequently associated with lower esophageal rings and may play a role in their pathogenesis; 2. the radiologic finding of a ring should serve as a clue to the possibility of esophageal reflux and 3. long-term control of dysphagia in these patients may depend upon control of the associated reflux as well as mechanical disruption of the ring.

INTRODUCTION

The lower esophageal ring (Schatzki's ring) is a thin, circumferential ridge located at the squamocolumnar junction of the distal esophagus.[1, 2] It is most easily detected radiologically in the presence of a hiatus hernia[1, 3] and is found in up to 14% of upper gastrointestinal x-rays.[4] Although in many cases it causes no symptoms,[5] rings with diameters less than 13 mm.[5] frequently cause progressive solid dysphagia or episodic aphagia i.e., intermittent complete obstruction of the esophagus by a food bolus usually lasting only a few minutes and relieved by vomiting or swallowing liquid ("steakhouse syndrome").[1, 3, 6, 7]

The clinical-pathologic studies of Goyal and his co-workers[2] have clarified the nature and location of the lower esophageal ring and helped differentiate it from muscular rings[7] and membranous webs located more proximally. The pathogenesis, however, of these rings is unknown. We have recently observed the progressive narrowing of an originally asymptomatic ring to one producing episodic aphagia in a patient with long-standing reflux esophagitis. This interesting case prompted a review of recent experience at this hospital and an analysis of 18 patients seen during the past 10 years has suggested a strong association between the presence of a ring and esophageal reflux.

REVIEW OF PATIENT RECORDS

The records of 427 patients hospitalized between 1 January 1966 and 31 December 1975 accessioned under H-ICDA* code numbers 530.3 and 750.3 and ICDA-8† code numbers 539.3 and 756.3 were reviewed. Included under these headings are all types of obstruction of the esophagus,

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From the Division of Gastroenterology, Department of Medicine, University of California, San Francisco.

* Hospital International Classification of Diseases Adapted.

† International Classification of Diseases Adapted.

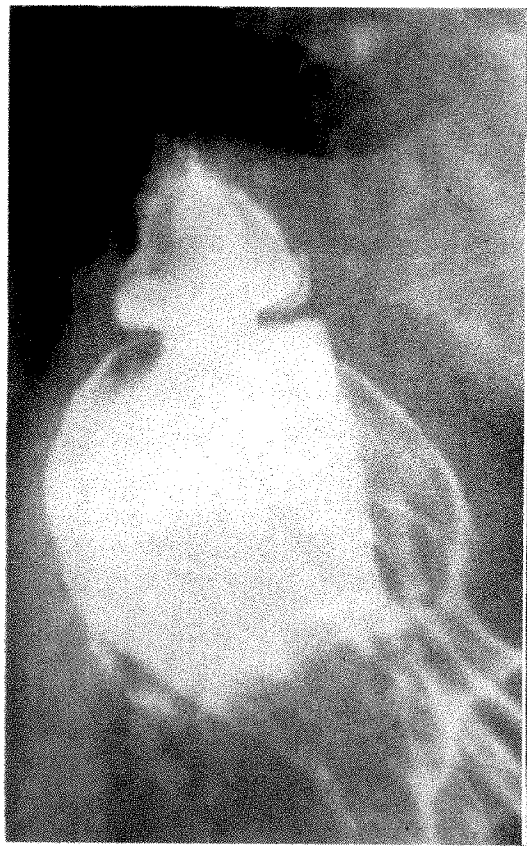

Fig. 1a

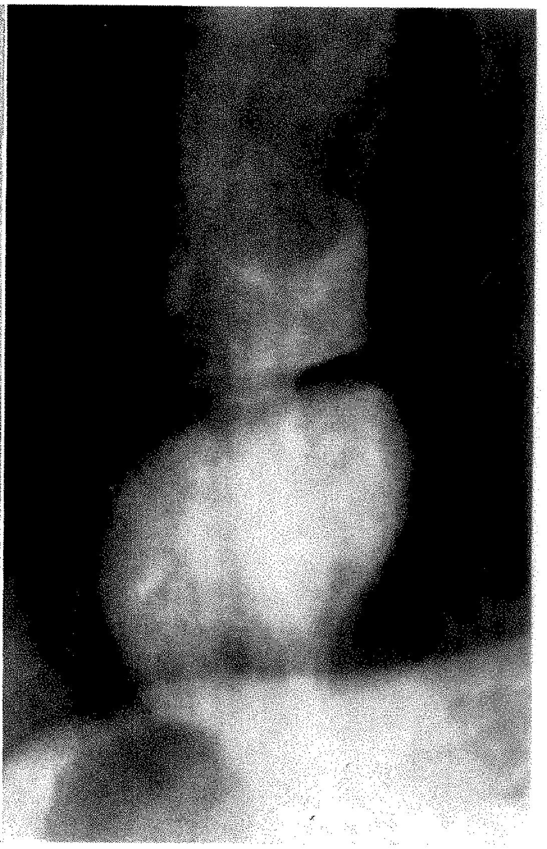

Fig. 1b

Figs. 1a and 1b—Both lower esophageal rings shown (Fig. 1a, Case 1; Fig. 1b, Case 2) were accompanied by symptomatic and endoscopically documented reflux esophagitis and were treated successfully with bougienage. The radiologic findings in these two patients were typical of those in this series.

both congenital and acquired. Only cases in which review of x-rays and/or operative reports confirmed a thin membranous constriction at the lower end of the esophagus were included in this series. All films showed findings similar to those in Figures 1a and 1b and matched the radiologic description published by Schatzki and Gary:[3, 8] a thin ($\leq$ 4 mm.), more or less symmetrical, diaphragm-like narrowing of the lower esophagus, oriented perpendicularly to the long axis of the esophagus, accompanied by a hiatus hernia and located no more than 5 cm. above the diaphragm. In each of the cases confirmed surgically, the operative note clearly described a thin ring located in the region of the squamocolumnar junction. Endoscopic findings accepted as evidence of esophagitis included erythema and friability of the esophageal mucosa, superficial erosions, or frank ulceration.[9] The presence of leucocytes in the surface epithelial layer was considered histologic evidence of esophagitis.[9]

Data from the 18 cases are summarized in Table I. In 16 of these patients, the presence of a ring was confirmed endoscopically (10 cases) and/or surgically (seven cases). In five patients endoscopy failed to demonstrate rings which were seen on x-ray or at surgery. These endoscopies were generally performed using the earlier rigid scopes which make air insufflation with adequate distention and visualization of the distal esophagus more difficult than with the currently used flexible endoscopes. Evidence of reflux was present in 16 of these 18 patients and included at least one of the following: overt esophagitis noted at endoscopy or surgery (14 cases), histologic evidence of esophagitis (three cases), or a history of bothersome pyrosis or free reflux (defined as regurgitation of bitter fluid or food when recumbent or bending over) obtained by at least two interviewers usually prior to x-ray examination (13 cases). Difficulty in swallowing was noted by 16 patients but only six complained of episodic aphagia ("steakhouse syndrome"), the symptom often considered characteristic of lower esophageal rings.[1, 3, 6, 10] As has previously been noted in patients with reflux,[11] there was marked variation in the duration of these symptoms as well as the sequence in which they appeared. This series was also typical of previously reported patients with lower esophageal rings in that the number of males (10 cases) and females (eight cases) was nearly equal[8, 10] and dysphagia usually first appeared after the age of 50.[1, 8, 10, 12] In six patients, symptoms of esophageal reflux preceded dysphagia by eight months to 10 years.

Surgery was performed in nine cases and consisted of hiatal hernia repair (nine cases), usually with wedge resection or finger fracture of the ring (seven cases). Histologic examination of the resected rings showed chronic inflammation with lymphocytes and plasma cells in the subepithelial tissue. The remaining nine patients were treated by dilitation. Most recent cases were treated by the sequential passage of one small (French no. 16-18) followed by one large (French no. 44-50) bougie.[1] The patients' symptoms of dysphagia generally responded well to either operative or non-operative therapy, although recurrences were noted in both groups.

Two cases for which follow-up information was available suggest that the long-term control of symptoms may depend upon control of reflux as well as mechanical disruption of the ring. In one patient with persistent endoscopic evidence of esophagitis (Case 8), a symptomatic ring recurred four times over a period of six years and was treated successfully each time with bougienage. In another patient with long-standing reflux (Case 1), serial x-rays and endoscopies, performed over a period of four years, documented the progressive narrowing of an originally asymptomatic ring 16 mm. in diameter to one 12 mm. in diameter causing episodic aphagia.

The demonstration of an association between the presence of a lower esophageal ring and reflux would be important for several reasons. It would suggest that long-standing reflux may play a role in the pathogenesis of the lower esophageal ring and indicate that reflux esophagitis should be aggressively looked for and perhaps treated in patients with symptomatic rings. This relationship between reflux esophagitis and the lower esophageal ring has in the past been a matter of dispute. Several investigators have noted that reflux and a ring may coexist in some cases[7, 8, 13-15] or found histologic evidence of chronic inflammation in resected rings.[16] Other investigators have not found these histologic changes and have emphasized the lack of reflux symptoms in most patients.[1, 10, 17]

Most published information about the lower esophageal ring has been accumulated from patients initially undergoing radiologic or endoscopic examination for a variety of gastrointestinal complaints. Such findings, including those reported here, are naturally skewed to include patients with symptomatic rather than asymptomatic

TABLE 1

Case no.	Age	Sex	Duration of symptoms (months)				Confirmation of ring			Evidence of esophageal reflux			Treatment
			Free reflux	Pyrosis	Dysphagia	Episodic aphagia	X-ray	Endoscopy	Surgery	Esophagitis on endosc.	Esophagitis at surgery	Esophagitis on biopsy	
1	76	F	4	144	48	2	X	X		X			Bougienage
2	66	M	240		120		X	X					Bougienage
3	48	F		60	12		X			X			Bougienage
4	64	F	18	8	10		X			X			Bougienage
5	47	F		3			X	X		X			Bougienage, Hiatal hernia repair
6	62	M					X	X		X			Hiatal hernia repair
7	65	M		240	120	120	X	X		X			Bougienage
8	50	M		12	2	180	X	X		X			Bougienage
9	52	M				180	X		X	X	X		Disruption of ring & Hiatal hernia repair
10	51	M		48	48		X		X	X	X	X	Disruption of ring & Hiatal hernia repair
11	41	F	12	30	12		X		X				Disruption of ring & Hiatal hernia repair
12	44	M				60	X		X				Disruption of ring & Hiatal hernia repair
13	37	F				156	X		X	X	X	X	Disruption of ring & Hiatal hernia repair
14	36	M		60	72		X		X		X		Disruption of ring & Hiatal hernia repair
15	48	M		48	48		X	X	X	X		X	Disruption of ring & Hiatal hernia repair
16	52	M		9	9		X	X		X			Bougienage
17	70	F	48	48	240		X	X		X			Bougienage
18	68	F			24		X	X					Bougienage

rings and may also suggest an artifactual association between rings and a variety of other gastrointestinal disorders. Nonetheless, the fact that 16 of 18 consecutive patients with lower esophageal rings in this series had evidence of reflux strongly suggests a real association between the two entities. Furthermore, although these findings are most applicable to patients with symptomatic rings, it is unlikely that symptomatic and asymptomatic rings represent different entities since they are radiologically and morphologically identical[2, 8] and silent rings may narrow sufficiently to cause dysphagia if followed long enough.[5, 15] A second potential difficulty with this series is that, except in the operated cases, the location of the ring was not confirmed (by biopsying the superior and inferior surface) to be the squamocolumnar junction. Congenital webs, however, located above the squamocolumnar junction are relatively uncommon[18] and the x-ray and endoscopic findings in this series were typical of those described by others. Furthermore, since few patients with lower esophageal rings are subjected to operation or biopsy of the superior and inferior surfaces of the ring to confirm its location, these findings should be generally applicable.

Thus, these findings suggest striking association between lower esophageal rings and esophageal reflux. They also suggest that reflux may play a role in the pathogenesis of some rings and that long-term control of dysphagia in these patients may depend upon control of the associated reflux as well as mechanical disruption of the ring. Furthermore, the presence of a ring on x-ray should alert the physician to the possibility of esophageal reflux.

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Communication from Abroad

Jejunal Bile Salts and Microflora in Patients with Partial Gastrectomy

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Bile acids and microflora were studied in the proximal jejunum in 31 patients with Billroth I or II gastrectomy. At least 10^5 bacteria/ml., most frequently aerobic or facultative aerobic organisms, were isolated in 25 patients.

Deconjugation diminished considerably in only three of seven patients with bile salt deconjugation treated with clindamycin. The relationship between bacterial overgrowth, deconjugation, steatorrhea, cholesterolemia and the relationship between bile salt concentration after testmeal and steatorrhea, are discussed. Bacterial overgrowth and bile salt deconjugation are only minor causes of steatorrhea in this series.

Malabsorption in patients with partial gastrectomy has many causes. One of these is bile salt deconjugation by bacterial overgrowth in the small intestine. Only conjugated bile salts with their specific stereochemical structure are able to form mixed micelles. By bacterial deconjugation the intraluminar concentration of conjugated bile salts can drop below the critical micellar level of 5 μmol/ml. causing steatorrhea.

MATERIAL

A selected group of 31 gastrectomized patients (29 men and two women) aged 30-72 years, were studied.

The study was performed from three to 32 years postoperatively, with a mean of 14 years. The mean preoperative age was 35 years. Sixteen patients had a Billroth I partial gastrectomy. Six were reoperated: vagotomy in five, conversion to Billroth II plus vagotomy in one patient.

Fifteen patients had a Billroth II partial gastrectomy. Later a conversion to Billroth I was performed in four, associated with thoracal vagotomy in two. Seven patients had no complaints, seven suffered from diarrhea and dumping, six from dumping, four from diarrhea alone, ten from the small pouch syndrome, five from biliary reflux, three from serious malnutrition, three from gastritis, two from afferent loop syndrome and one from peptic ulcer.

METHODS

Procedure:—In a first investigation jejunal fluid specimens were obtained by

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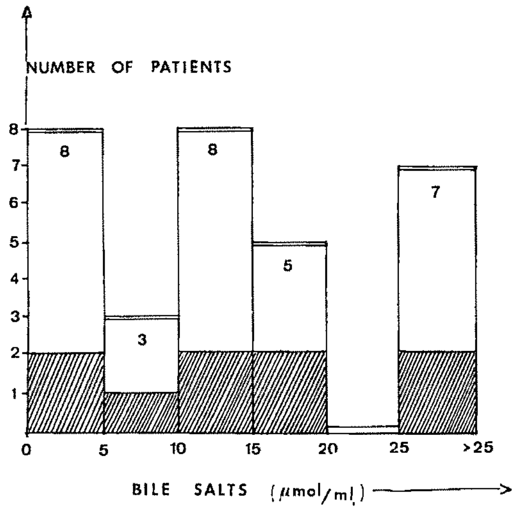

Fig. 1—Fasting bile salt concentration in the proximal jejunum. Cross-hatched bars represent the nine patients with bile salt deconjugation.

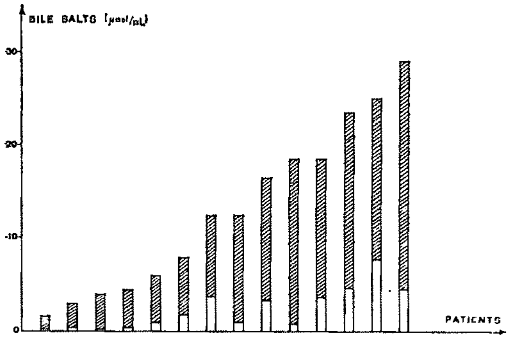

Fig. 2—Bile salts after test meal in 14 patients. The clear bars represent free bile acids, the cross hatched conjugated bile acids.

intubation under fluoroscopic control after an overnight fast. Samples were aspirated, 90 and 120 cm. aborally, in the proximal jejunum and examined for total bile salt concentration, thin-layer chromatography and intestinal microflora.

Clindamycin, 4 times 150 mg. a day, was administered to seven of the nine patients with bile salt deconjugation. After one week a small intestinal intubation followed for bacteriological and bile salt analysis.

Six patients with deconjugation and four without deconjugation had a second bile salt collection during 10 and 20 minutes after intravenous pancreozymin (Boots 100 U.). In these ten patients and in another four, a third small intestinal intubation was performed with intragastric infusion of a 225 ml. test meal, containing 200 ml. of Travamin® (10 gm. of casein hydrolysate and 10 gm. dextrose), 15 gm. lecithin, 5 ml. of corn oil and 10 ml. of *tinctura fortis aurantii corticis*. Three hours before this investigation all subjects had a standard breakfast consisting of a sandwich and one egg. Bile salts were examined in samples aspirated in the proximal jejunum 10 and 20 minutes after intravenous pancreozymin, also 15 and 30 minutes after intragastric infusion of the test meal.

In all 31 subjects serum cholesterol[1] and fecal fat[2] (normal < 5 gm. daily under a diet of 60 gm. of fat daily) were measured.

Bile salt determination:—All samples of intestinal juice were extracted first.[3, 4] Bile salts in jejunal fluid were separated by thin-layer chromatography[5] and quantitative measurements carried out using 3 α hydroxysteroid dehydrogenase (Worthington).[6]

Bacteriology:—Fasting jejunal samples were cultured not later than 10 minutes after collection. After preparing serial dilutions of the fluid, aliquots were spread on blood agar, Eosin Methylene Blue Agar (Difco), Tomato Juice Agar (Difco) and Blood Agar with 100 µgm. of neomycin/ml. Aerobic organisms were cultured for 48 hours, the anaerobic organisms for 48 hours in a Gas Pak System (BBL).

Organisms of interest were isolated in pure subculture and subjected to further tests to confirm their obligate or facultative

TABLE I

FREQUENCY OF ISOLATED ORGANISMS IN THE PROXIMAL JEJUNUM

Microflora	
Increased concentration ($\geqq 10^5$ bacteria/ml.) : 25/31	
Aerobes	11
Aerobes + facultative anaerobes	10
Fac. anaerobes	1
Aerobes + fac. anaerobes + strict anaerobes	2
Aerobes + strict anaerobes	1
Differentiation	
Aerobes: Gram negative	
E. coli	13
Klebsiella	3
Proteus	3
Pseudomonas	2
Gram positive	
α *Streptococcus*	7
Lactobacillus	7
β *Streptococcus*	5
γ *Streptococcus*	2
Fac. anaerobes:	
Streptococcus	11
Diphtheroids	2
Lactobacillus	1
Strict anaerobes:	
Clostridia	2 ($< 10^5$/ml. in 3)
Corynebacteria	2 ($< 10^5$/ml. in 2)

anaerobic nature. Each organism was counted and expressed as number/ml. of duodenal fluid.

RESULTS

Bile salts:—The range of the fasting bile salt concentrations in the jejunum, 120 cm. aborally is shown in Fig. 1. The mean concentration was 12.9 μmol/ml. (range: 0.25 μmol/ml.). In nine of 31 patients bile salt deconjugation was found.

After pancreozymin, the mean volume and concentration of the first 10-minute collection were 50 ml. and 37.3 μmol/ml. (range: 12-95 μmol/ml.) respectively. Of the second 10-minute collection they were 40 ml. and 26.7 μmol/ml. (range: 7-60 μmol/ml.).

The results after the test meal in 14 patients are represented in Fig. 2. The mean concentration was 13 μmol/ml. (range: 1.7-29 μmol/ml.). The percentage deconjugation ranged from 4-31%. The ratio of glycine to taurine conjugated bile salts was on average 2.9.

Microflora:—A concentration of at least 10^5 bacteria/ml. was found in 25 of the 31 patients. An increase of aerobic bacteria was noticed in all patients except one, of gram positives in 20 and of gram negatives in 13. Increased concentrations of facultative anaerobes were obtained in 13 patients and of strict anaerobes in three patients (Table I). The bacterial concentration in seven patients with bile salt deconjugation and the response to treatment with clindamycin are shown in Table II. The aerobic flora are identical in the patients with and without bile salt deconjugation. All three patients with increased strictly anaerobic flora present bile salt deconjugation. All seven patients still have a bacterial concentration higher than 10^5 germs/ml. after treatment with clindamycin. The aerobic flora practically do not change in one patient but up to 10^5 *Candida*/ml. appear. The facultative anaerobic flora remain increased in two of four patients. The strict anaerobes disappear from the small intestine in all but one patient (F. E.), where 10^4 bacteroides/ml. appear. In patient R. A. anaerobes and deconjugation disappear simultaneously. In patient A. A. deconjugation diminishes considerably, without apparent change of the flora. In patient F. E. deconjugation decreases but 10^4 bacteroides/ml. appear. In the four remaining patients deconjugation is still present, in spite of the disappearance of all strict anaerobes in C. M. and V. D. W.

TABLE II

MICROFLORA AFTER CLINDAMYCIN

Patient	*α-γ Streptococcus*	*β Streptococcus*	*Staphylococcus*	*Lactobacillus*	*E. Coli*	*Klebsiella*	*Proteus*	*Pseudomonas*	*Neisseria*	*Candida*	*Streptococcus*	Fac. an. Lactob.	Fac. an diff.	*Clostridia*	*Bacteroides*	*Corynebacteria*	Deconjugation
A. A.	(3)		(3)							(1)	5						+++
after clindamycin	(4)				(4)						5						+
C. M.		(4)		6	6											5	+
after clindamycin	(4)								(4)	5			(3)				+
F. E.	5				5		(4)										+
after clindamycin					5	5	5								(4)		±
L. W.			5	5				6		5	5						+
after clindamycin			6								5						+
R. A.					6	6					5			5		5	+
after clindamycin		5		(4)	5	(4)						(4)					−
V. D. W.				6		5	6				5			5			++
after clindamycin	5			5	5												++
V. E. L.	(4)	(3)							5								++
after clindamycin	(4)		(4)						5		(4)						+++

Data are recorded as the $\log_{10}$ of the counts of organisms/ml. of small intestinal fluid. Numbers in parentheses are the most significantly increased counts. At the right, the semiquantitative estimation of deconjugation.

TABLE III

RELATIONSHIP BETWEEN FOUR PARAMETERS

	Deconjugation	Steatorrhea	Chol. ↓	Bacterial overgrowth
Deconjugation	$\boxed{9}$	4	2	9
Steatorrhea	4	$\boxed{11}$	4	10
Cholesterol ↓	2	4	$\boxed{10}$	7
Bact. overgrowth	9	10	7	$\boxed{25}$

The numbers in squares represent the frequency of the parameters examined.

Steatorrhea—cholesterolemia:—In 11 patients steatorrhea, ranging from 6.2-13.2 gm./24 hr. with a mean of 9.1 gm./24 hr., is observed. Hypocholesterolemia is found in ten patients (Table III). Relationships between deconjugation, steatorrhea, cholesterolemia and bacterial overgrowth are summarized in Table III.

If the 25 patients with bacterial overgrowth, nine patients present deconjugation and ten steatorrhea. Four of the nine patients with deconjugation have steatorrhea. Four of the 11 patients with steatorrhea present hypocholesterolemia. No significant difference is found in deconjugation, microflora and steatorrhea, between Billroth I and Billroth II resections (Table IV).

Relationship between jejunal bile salt concentration after test meal and steatorrhea was analysed in 14 patients. Five patients present steatorrhea. In three a conjugated bile salt concentration below the critical micellar concentration was found. In the two others a strongly accelerated transit or jejunitis was confirmed by radiology and/or biopsy. The patient with the lowest total bile salt concentration (1.7 μmol/ml.) after test meal had no steatorrhea.

COMMENT

In Billroth I gastric resection a bacterial concentration higher than the normal counts of 10^4 organisms/ml.[7-10] can be explained by the disappearance of the gastric acid secretion with its bactericidal properties,[7, 10] in Billroth II resection also by stasis in the afferent loop.[12-16] A shift of the flora from gram positive to gram negative organisms also occurs. Meanwhile anaerobes may appear in pathological concentrations (over 10^4 bacteria/ml.), the normal small intestinal flora being predominantly aerobic.[9, 17-19] Recently however anaerobes were also observed in the normal small intestine, especially after contamination by food and saliva.[19]

In 25 of our 31 patients we observed elevated fasting bacterial concentrations, as frequently after Billroth I as after Billroth II resection. In our study the flora mainly consisted of such aerobic gram positive types as coliforms, klebsiella, proteus. The number of patients with increased concentrations of strictly anaerobes is remarkably low, namely three. Indeed, a dominant anaerobic flora was reported in bacterial overgrowth of the small intestine.[10, 11, 19-21] The small number of anaerobes observed in some other studies was mostly due to defi-

TABLE IV

COMPARISON BETWEEN BILLROTH I AND BILLROTH II RESECTION IN 21 PATIENTS WITHOUT REINTERVENTION

(n)	Bacteria	Deconjugation	Steatorrhea	Cholesterol ↓
B_I : 10	6	2	2	3
B_{II} : 11	8	4	3	3

cient culture technics. In our study, however, we isolated massive concentrations of anaerobes in the stools, which seems to confirm the reliability of the method used.

Bile salt deconjugation was found in only nine of the 25 patients with bacterial overgrowth. Indeed, contamination appears to cause deconjugation in some cases only[8, 19] and the organism responsible for the deconjugation can only definitely be demonstrated *in vitro*. Deconjugation was observed with most anaerobes, but with some aerobes too such as streptococcus, staphylococcus, lactobacillus and klebsiella.[10, 22] The relatively small number of anaerobes isolated in our patients suggests that aerobes were also responsible for deconjugation. For treating bacterial overgrowth of the small intestine, one should use antibiotics which also affect the anaerobes such as tetracyclin,[10, 23] lincomycin or clindamycin,[13, 17, 26] or even ampicillin.[25] After clindamycin we observed the disappearance of strict anaerobes but deconjugation remained unchanged in four of the seven treated patients. Perhaps a treatment period of seven days is too short or the dosage of 600 mg./day is too low. Most probably *in vitro* isolation of the deconjugating germ, followed by administration of the antibiotic according to the antibiogram, is a more reliable procedure. The function of bile salts in forming mixed micelles, solubilization and absorption of monoglycerides, fatty acids, cholesterol and phospholipids is documented by several authors.[10, 11, 26-29] The wide range of the total bile salt concentration after a meal (between 1.7 and 29 μmol/ml.) was also observed by other authors.[27, 30]

Bile salt deconjugation by bacterial overgrowth certainly plays an important role in steatorrhea. Indeed, toxicity of free bile salts on the small intestinal mucosa causing malabsorption of free acids, was emphasized by some authors.[31-33] Small intestinal lesions were described on electron microscopy in stagnant loop syndrome.[31] Others, however, demonstrated that peroral administration of free bile salts did not inhibit fat absorption[35, 36] in rats and did not provoke steatorrhea[10] or mucosal lesions in man.[37] Finally, several authors observed no mucosal lesions in stagnant loop syndrome.[32, 38-40] In our study only four of nine patients with deconjugation presented steatorrhea. In addition a low level of deconjugation was observed in patients with and without steatorrhea. Furthermore overgrowth alone can hardly be proposed as the principal cause of steatorrhea, because only 10 out of 25 patients with bacterial contamination presented steatorrhea. This absence of relationship is confirmed by other authors.[8, 10, 16] It is also important to note that bacteria do not inactivate pancreatic lipase[32, 41] and that in patients with stagnant loop syndrome, steatorrhea disappeared after administration of conjugated bile salts, in spite of high free bile salt levels in the small intestine.[40-41] Most authors agree that a conjugated bile salt level below the critical micellar concentration is an important cause of steatorrhea in bile salt deconjugation by bacterial overgrowth.[10, 11, 41, 42] We assume that steatorrhea in three patients with low bile salt concentration after test meal, may be ascribed to this mechanism.

In some cases lesions of the jejunal mucosa are responsible. Other important factors contributing to steatorrhea in partial gastric resection are an accelerated transit time with deficient contact between food mass and mucosa[43] and an inappropriate timing of the release of bile and pancreatic juice into the small intestine to the arrival of food mass.[43-45] Several of these factors probably enhanced steatorrhea in eight of our 11 patients with steatorrhea and could even be demonstrated in some of them.

In patients with a slightly reduced bile salt pool, the bile stocked overnight in the gallbladder still contains a normal concentration of bile salts. But the concentration is decreased at the moment of the next gallbladder contraction after a second meal.[46] The finding of normal fasting serum bile salt levels in patients with partial gastrectomy (0.6-3.8 μmol/ml.; mean 1.85 μmol/ml.; n = 20) (unpublished data) seems to be an argument in favor of a normal or subnormal total bile salt pool in these patients. Thus a significant reduction of total bile salt pool is probably seldom the main cause of steatorrhea.[47]

In our patients the mean steatorrhea was mild and lower than in several other studies.[15, 48] A more severe degree of steatorrhea after Billroth II than after Billroth I[16, 49, 50] was not confirmed in our study.

The relationship between the upper jejunal bile salt concentration and cholesterolemia is complex. Bile salts inhibit cholesterol synthesis in the gut[29, 51] and in the liver[27] but they also are necessary for solubilization and absorption of cholesterol[27, 29, 41] and as a substrate for cholesterol synthesis.[11, 49] Thus an increased bile salt synthesis decreases cholesterolemia. Probably this mechanism has contributed to hypocholesterolemia in some of our patients.

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Communication from Abroad

Clustering of Different Subtypes of Hepatitis B Surface Antigen in Families of Patients with Chronic Liver Diseases

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Clustering of hepatitis B surface antigen (HBsAg) with both subtypes adr and adw in three families of patients with chronic liver diseases or hepatocellular carcinoma was demonstrated in Taiwan where adw is the main subtype. The subtype in the children was similar to that in their mothers, suggesting maternal transmission. In all the family units clustered with different subtypes, the same pattern occurred, invariably with fathers carrying HBsAg/adr and the children carrying HBsAg/adw. The subtype difference clearly rules out the transmission of hepatitis B virus (HBV) from father. Horizontal infection with the locally dominant adw-subtyped HBV in the children of fathers carrying HBsAg/adr explains the discrepancy of the subtypes in these families. Clustering of two HBsAg-positive brothers with hepatocellular carcinoma in one of the families was found. That both adr-subtyped and adw-subtyped HBV are capable of inducing chronic active hepatitis in another family suggests that host factors are probably more important in determining the clinical course of HBV infection.

INTRODUCTION

Hepatitis B is a highly infectious disease but the exact mode of natural transmission is not yet quite clear. The etiological agent has long been regarded to be a virus. Demonstration of hepatitis B surface antigen (HBsAg) as a marker of hepatitis B virus (HBV)[1, 2] has contributed to the progress in the study of transmission of HBV. In family members, close contacts and similar host factors probably afford the highly infectious HBV a suitable environment for transmission. Actually, familial clustering of HBsAg was demonstrated first by Blumberg, et al[3] soon after the discovery of HBsAg and has been confirmed repeatedly.[4-11] Subtyping of HBsAg is a useful epidemiological tool,[12] since the subtype is determined by genomes of HBV rather than the host.[13] Studies on the subtypes of HBsAg in HBsAg-clustered families usually revealed a similar subtype in the carriers of the same family with few exceptions,[8-10, 14-16] suggesting spreading of HBV probably from the same source in the family. To our knowledge, there have been only a limited number of families clustered with different subtypes of HBsAg.

In addition to HBsAg clustering, increased frequencies of chronic liver diseases and hepatocellular carcinoma have also been demonstrated in such families.[17, 18]

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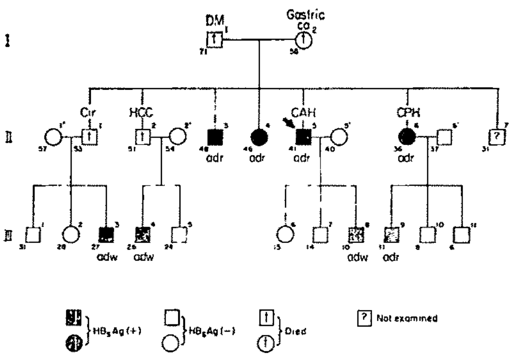

Fig. 1—Family 1. Clustering of carriers with different subtypes of HBsAg, adr and adw; chronic active hepatitis (CAH), chronic persistent hepatitis (CPH), cirrhosis of the liver (Cir) and hepatocellular carcinoma (HCC).

During the past two years of studying intrafamilial infection of HBV in Taiwan, we have found 24 families clustered with HBsAg; some of the family members also had increased frequencies of chronic liver diseases. The subtype was the same in 21 families, 15 of which have been presented previously.[10] In the remaining, the three families clustered with different subtypes of HBsAg are considered epidemiologically significant and will be presented.

FAMILIES AND METHODS

The probands and their family members:—The probands were patients admitted to Department of Internal Medicine, National Taiwan University Hospital because of chronic liver diseases or hepatocellular carcinoma. The family history was obtained from the proband and the familial relationship was further checked by typing ABO blood groups.

Detection and subtyping of HBsAg:—HBsAg was detected with solid phase radioimmunoassay (Ausria II-125, Abbott Laboratories, North Chicago, IL) and the positive sera were subtyped for major antigenic determinants with the hemagglutination inhibition method after Imai, et al.[19] Briefly, 25 μl. of serum specimen to be tested was serially diluted in a microtiter plate (Cooks Engineering Co., Alexandria, VA) and to each well two hemagglutination units of monospecific antibody to the antigenic determinant were added. After incubation, 25 μl. of 0.6% glutaraldehyde-fixed sheep erythrocytes coated with HBsAg bearing the corresponding specificity were added. Hemagglutination inhibition in the tested serum indicated the presence of the specific determinant.

In the first and the second families, all the test sera were assayed once except in the patients with liver diseases, whose sera were assayed at least twice with an interval of 12 months in the first family and three months in the second family. In the third family, all members were tested twice with an interval of 17 months.

RESULTS

Family 1 (Fig. 1):—The proband (II-5) was a 41-year old male with chronic active hepatitis and carrying HBsAg/adr. His father died of diabetes mellitus at age of 71 years and his mother died of gastric cancer at age of 58 years. At least three of his siblings (II-3, II-4, II-6) were also carrying HBsAg/adr; one of them (II-6) suffered from chronic persistent hepatitis with mildly elevated serum transaminase activity for more than one year. Two elder brothers died of liver diseases intimately related to HBV; one (II-1) died of cirrhosis of the liver and another (II-2) of hepatocellular carcinoma at the age of 53 and 51 years respectively. The remaining siblings were apparently healthy except the youngest brother who was unavailable for the study but was said to be ostensibly well. Their spouses were all healthy and none was an HBsAg carrier. Clustering of HBsAg was also present in the third generation; four (III-3, III-4, III-8, III-9) out of 11 were asymptomatic carriers. Both

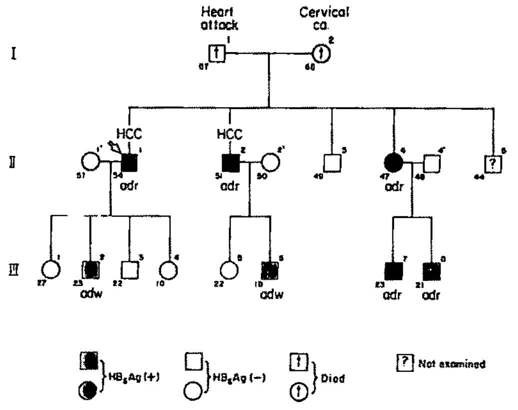

Fig. 2—Family 2. Clustering of carriers of HBsAg/adr and HBsAg/adw in a family with two patients of hepatocellular carcinoma (HCC).

HBsAg/adw and HBsAg/adr were carried in this generation. One of the children (III-8) of the carrier father (II-5) was carrying HBsAg/adw which was different from the father's (HBsAg/adr). While one of the sons (III-9) of the carrier mother (II-6) had the same subtype (HBsAg/adr) as the mother's. All the members in the third generation were asyptomatic and denied any episode of liver disease in the past. Repeated testing of HBsAg and its subtype in those with chronic liver diseases (II-5, II-6) during interval of 12 months always yielded consistent results.

Family 2 (Fig. 2):—The proband's father (I-1) died of a heart attack at 67 years of age and the mother (I-2) died of cervical cancer at 68. Both the 54-year old proband (II-1) and his 51-year old brother (II-2) had hepatocellular carcinoma which manifested almost simultaneously in September, 1976 and the diagnosis was confirmed by histology. The proband did not have coexisting cirrhosis and was subsequently treated with a hepatic lobectomy, while his younger brother had well-established macronodular cirrhosis and was not operated upon. Both were positive for HBsAg with the subtype of adr. Their only sister (II-4) was also an asymptomatic carrier with HBsAg/adr, while their younger brother (II-3) was negative for HBsAg. The youngest brother (II-5) was unavailable for study but was said to be healthy. The spouses were apparently well and none appeared to be HBsAg carriers. One of the children (III-2) of the proband was also a carrier but the subtype was different, being adw rather than adr. A similar situation also occurred in the family of his younger brother (II-2) who had hepatocellular carcinoma with cirrhosis. On the other hand, the two sons (III-7, III-8) of carrier sister (II-4) both had the same subtype as the mother (adr). All the members in the third generation were asymptomatic. Testing of HBsAg and the subtype, performed three months apart in the two brothers with hepatocellular carcinoma, gave consistent results.

Family 3 (Fig. 3):—The proband (II-1) was a 22-year old male with histology verified chronic active hepatitis. His father (I-1) had suffered from chronic liver disease for more than two years and was diagnosed as chronic active hepatitis with cirrhosis after needle biopsy and peritoneoscopy. All the remaining family members were apparently healthy and denied episodes of liver disease in the past except for the eldest sister (II-3) who had an episode of jaundice assumed to be due to viral hepatitis at age of three and recovered one month thereafter. Clustering of HBsAg was evident; the father had HBsAg/adr, while three out of five children (II-1, II-2, II-5) had HBsAg/adw. The mother (I-2) was apparently healthy and negative for HBsAg. The result of HBsAg testing and subtyping remained unchanged in the follow-up survey held 17 months later.

COMMENT

Family clustering of HBsAg has been demonstrated in different parts of the

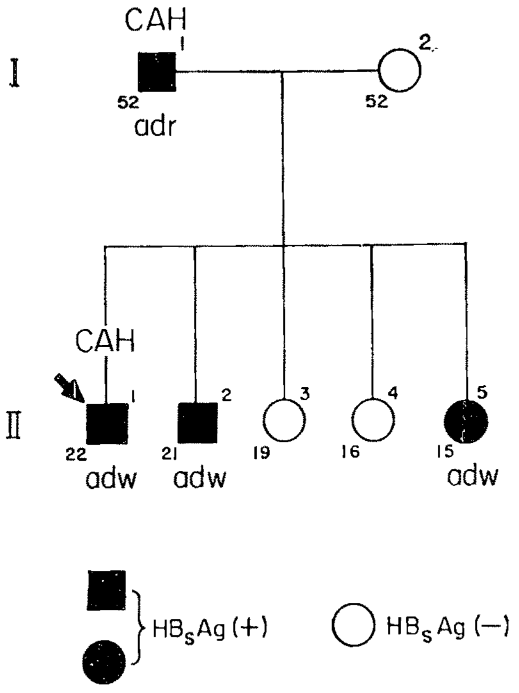

Fig. 3—Family 3. Clustering of carriers of HBsAg/adr and HBsAg/adw in a family with two patients of chronic active hepatitis (CAH).

world[3-11, 14-16] and is more common where the carrier rate is high.[8] Vertical transmission from carrier mothers to their children has been shown to occur in 40% of such deliveries in Taiwan, whereas transmission from carrier fathers has been considered unlikely.[14] The first two families clustered with HBsAg in this study clearly show the possibility of maternal transmission which is further suggested by the similar subtype in the antigenemic children and their carrier mothers. Our previous observation has also revealed an increased prevalence of antigenemia in the children of carrier fathers[10] and this is observed again in this study. Six out of 14 children (42.9%) of four carrier fathers were also carriers of HBsAg, showing an increased prevalence of antigenemia despite the fact the subtypes of HBsAg were not the same between the carrier fathers and carrier children. The two brothers in Family 1 who died of cirrhosis and hepatocellular carcinoma might have also been carrying HBsAg as their siblings did, since the two diseases they succumbed to have been shown to be highly prevalent for HBsAg in Taiwan (89.7% for cirrhosis and 91.2% for hepatocellular carcinoma by radioimmunoassay).[20] Two out of five children (40%) of these two died brothers were also asymptomatic carriers with HBsAg/adw.

It is noteworthy that in all the family units clustered with different subtypes of HBsAg, a similar pattern occurred invariably. All were fathers but not mothers, carrying HBsAg/adr, while the children carried HBsAg/adw. The difference in subtypes clearly rules out the transmission of HBV from fathers in these families. The observation is consistent with the findings revealed by Mazzur, et al[16] in south central Bougainville. They found that of the 12 families in which the mother was HBsAg-positive, only one had mixed subtypes; while among the six families in which the father was the only parent positive for HBsAg, there were four families with mixed subtypes. In addition, the only family reported by Szmuness, et al[15] also had a similar pattern in subtype distribution as in our three families. Chronic carriage of HBsAg has been proposed by Blumberg, et al[3] to be due to the inherited susceptibility to chronic HBV infection with a simple autosomal recessive trait. The children of either a carrier father or mother thus equally inherited the susceptibility to persistent infection. When a child is born to a carrier mother, the persistent infection is most likely from the carrier mother due to the intimate biologic relationship between them[21] and thus it is not unexpected that both are carrying the same subtype of HBsAg. On the other hand, when a child is born to a carrier father, the father does transmit the susceptibility to the child but the chance of infection from the carrier father is much less frequent than that from the carrier mother. Since it has been shown that HBsAg/adw is far more common (91%) than HBsAg/adr in Taiwan,[10] horizontal infection with the locally dominant adw-subtyped HBV in the children of carrier fathers with HBsAg/adr probably explains the same pattern of dissimilar subtypes between the carrier fathers and their children in this study.

The study in the three families also confirmed familial clustering of both HBsAg and liver diseases including hepatocellular carcinoma,[17, 18] suggesting persistent HBV infection as probably one of the etiologic factors of these diseases. It is worth mentioning that in one of the families, two brothers were found to suffer from hepatocellular carcinoma which manifested almost simultaneously. The younger brother had coexisting cirrhosis in addition to the malignancy as in most of the liver cancer patients in Taiwan[22] but the proband did not have coexisting cirrhosis. If HBV is oncogenic, as proposed by Vogel, et al,[23] the observation makes us conclude that hepatocarcinogenesis by HBV is not necessarily accompanied with cirrhotic process.

Despite carrying different subtypes of HBsAg, that both the son and the father in one of the families suffered from chronic active hepatitis denotes that a similar injury in the liver can be induced by different strains of HBV. This is in keeping with the proposal of Dudley, et al[24] that in HBV infection, host response to the infective agent is of predominant importance in determining the clinical course rather than the viral factors.

Although the infection by HBV in these family members has been considered significant in the pathogenesis of the liver diseases including hepatocellular carcinoma, the possibility that other undiscovered etiologic factors are responsible still remains and requires further study.

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The Diagnostic Significance of the Immunoglobulin A to M and A to Total Ratios in the Pancreatoduodenal Fluid of Patients with Benign and Malignant Pancreatic Diseases

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Immunoglobulins A, M and G in the pancreato-duodenal fluid (PDF) of 35 pancreatic disease-free individuals and 48 patients with chronic pancreatitis (25), hypersecretory disorders (10), renal transplanted (4) and with pancreatic cancer (9), were determined by a single radial immunodiffusion method. Although a trend of immunoglobulin hypersecretion in benign diseases and hyposecretion in malignancies was present, individual levels of Ig-A and Ig-M differed statistically only between cancer and other groups. Calculating the ratios of Ig-A to Ig-M (A/M) and Ig-A to total immunoglobulin contents (A/T) in the PDF of patients with chronic pancreatitis or cancer, however, a significantly higher or lower ratio, respectively, was found compared to control group. Differences in A/M ratios could not be detected between patients with benign diseases, but were constantly present when these patients were compared to pancreatic cancer.

The underlying mechanism(s) of the disturbed immunosecretory system in pancreatic diseases remains speculative. Nevertheless, immunoglobulin measurements in the PDF of patients with pancreatic diseases offer a simple diagnostic aid in clinical differentiation of pancreatic pathology.

INTRODUCTION

There have been many reports evaluating serum immunoglobulin patterns in health, inflammatory disorders and neoplasms, yet the data for the major immunoglobulin classes are controversial and correlate poorly with the degree and progression of pathology.[1] Recently, attention has been directed both towards immunoglobulin concentrations in external secretions and to possible functions of the secretory immunoglobulin system.[2] The pancreas has been neglected in these studies, there being only isolated reports in the past.

This investigation is an extension of preliminary research in which it was shown that Ig-A and Ig-M concentrations in pancreatic cancer were significantly different from those observed in normal subjects as well as in patients with benign pancreatic disorders.[3] Attention has been directed to-

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TABLE I

IMMUNOGLOBULINS A AND M IN PANCREATO-DUODENAL FLUID*

		SIg-A	SIg-M	A/M	A/total
Group 1	Range mg./dl.	2.00-48.00	0.70-6.60	1.75-48.00	0.220-0.884
Normal	$\bar{X} \pm SD$	10.70 ± 9.18	1.60 ± 0.95	7.72 ± 7.50	0.35 ± 0.10
	Median	8.4	1	5.50	0.330
	P vs. Group 2	< 0.01	NS	< 0.001	< 0.01
	P vs. Group 3	NS	NS	NS	NS
	P vs. Group 4	NS	NS	NS	NS
	P vs. Group 5	NS	NS	< 0.001	< 0.05
Group 2	Range mg./dl.	5.10-48.00	0.10-4.00	7.00-66.00	0.220-0.800
Chronic pancreatitis	Median	10.8	1	10.83	0.390
	P vs. Group 3	NS	NS	NS	< 0.001
	P vs. Group 4	NS	NS	NS	< 0.005
	P vs. Group 5	NS	NS	< 0.001	< 0.01
Group 3	Range mg./dl.	3.20-12.00	0.40-2.10	2.86-28	0.100-0.380
Hypersecretory	Median	9.6	1.10	7.11	0.270
	P vs. Group 4	NS	NS	NS	NS
	P vs. Group 5	NS	NS	< 0.005	NS
Group 4	Range mg./dl.	4.00-28.00	0.40-3.00	3.50-28.00	0.200-0.600
Renal transplants	Median	8	0.90	9.23	0.270
	P vs. Group 5	NS	NS	= 0.01	NS
Group 5**	Range mg./dl.	0.10-64.80	0.50-24	0.05-56	0.003-0.660
Pancreatic cancer	Median	0.1	2	0.2	0.01

* Statistical analysis was done by the Mann-Whitney two-tailed rank test.
** Individual values in Table 2.

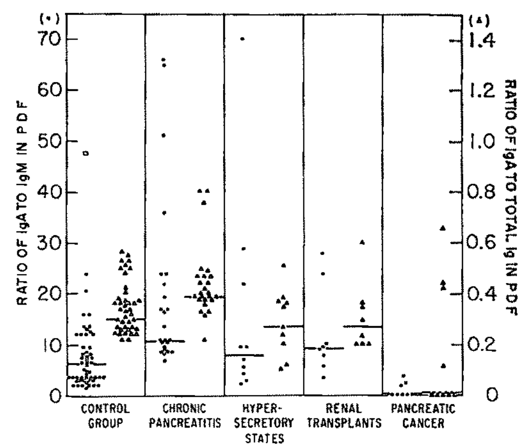

Fig. 1—Ig-A/Ig-M and Ig-A/TIG ratios of patients with and without pancreatic disease.

ward the Ig-A to Ig-M (A/M) and Ig-A to total immunoglobulin concentration (A/T) ratios, in order to determine whether in benign or malignant pancreatic diseases, an antigenic stimulus results in an operational "switch" of immunoglobulin secreting cells viz. Ig-A to Ig-M detectable in the pancreatic secretions by alterations in concentrations of immunoglobulins secreted.

Patients and Methods

One hundred and six determinations of A, M and G immunoglobulins in the pancreatoduodenal fluid (PDF) of 83 individuals were performed during a standard secretin test at the Mount Sinai Hospital Pancreatic Research Laboratory. Thirty-five patients with normal pancreatic function and past history free of complaints related to pancreatic disease and 45 patients with pancreatic disorders were allocated to five groups.

Group 1 included all 35 patients with normal secretin tests (17 males, 18 females age range between 28-68 years)—the control group.

Group 2 included 25 patients with proved alcoholic pancreatitis—the inflammatory group.

Group 3 consisted of 10 patients with pancreatic hypersecretion—these patients were studied to determine whether hypersecretion would alter immunoglobulin secretory patterns.

Group 4 compared four patients receiving immunosuppressive therapy following renal transplantation—these patients were studied to determine whether immunosuppression would alter immunoglobulin secretory patterns.

Group 5 consisted of nine patients in whom pancreatic malignancy was highly suspected. During posttesting laparotomy, the disease was proven and the extent of pancreatic cancer was established. In addition to the secretin test, all patients had a complete laboratory and clinical work-up.

The secretin test was performed according to standard technic.[4] Briefly, after a 12-hour fasting period, a double lumen gastroduodenal tube was positioned in the duodenum under fluoroscopic control.

Drainage was collected using intermittently negative suction of 90 mm. Hg. After initial collections of gastric and duodenal contents, 1 U./kg. of secretin (Warren-Teed) was given intravenously and samples were taken from the 20-minute basal as well as the maximal pancreatic outflow collection period. PDF samples were stored at −20° C for subsequent determination of immunoglobulins. After thawing, 5 ml. of PDF aspirates was concentrated 100x using a membrane diffusion (dialysis) technic with a cut-off point for proteins of less than 15,000 mw (Minicon, B15, Amicon Corp., Lexington, MA.). The concentration process usually required a 12-hour period and was carried out in a cold room. The recovered concentrates (40 μl.) were tested for immunoglobulin contents, with a radial single-immunodiffusion method, in monospecific antisera agar plates (Immunoplates III, Hyland,

TABLE II

INDIVIDUAL RATIOS OF IMMUNOGLOBULIN A TO M AND A TO TOTAL IMMUNOGLOBULIN CONTENTS IN PANCREATODUODENAL FLUID OF PATIENTS WITH PANCREATIC CANCER

A/M	A/total	Operative diagnosis
0.05	0.010	Multiple liver nodes, metastatic pancreatic cancer
0.05	0.010	Liver nodes, pancreatic cancer
0.05	0.010	Lung and liver metastatic pancreatic cancer
0.05	0.010	Diffuse carcinomatosis, liver metastasis
0.20	0.003	Liver metastasis, infiltration of duodenal wall
2.40	0.420	Cancer limited to the head of the pancreas
2.80	0.440	Cancer limited to the head of the pancreas
4.00	0.130	*Diffuse carcinomatosis, liver metastasis*
56.00	0.660	Cancer limited to the head of the pancreas

Costa Mesa, CA). All tests were carried out observing the manufacturer's instructions for the 48-hour "precision test". After determination of the individual immunoglobulin levels, the ratios A/M as well as A/T were calculated. These ratios with Ig-A as numerator were selected to detect changes in immunosecretory patterns reflected on the main immunosecretory gamma globulin.

Statistical analyses of the results were done with the two tailed Mann-Whitney rank test.

RESULTS

The immunoglobulin content of the PDFs tested and the calculated ratio data are summarized in Table I. Ig-A levels in the first group of patients (controls), ranged between 2 and 48 mg./dl. with a median value of 8.4 mg./dl. Ig-M ranged between 0.7 and 6.6 mg./dl., the median value being 1 mg./dl. Ig-A was found significantly elevated in chronic pancreatitis patients (Group 2), the levels ranged from 5.1-48 mg./dl., with a median value of 10.8, $P < 0.01$). The moderately increased levels of Ig-A in patients with hypersecretory disorders (Group 3) and kidney transplanted patients (Group 4) were not statistically different from controls (range and median, 3.20-12 mg./dl.-9.6 mg./dl. and 4-28 mg./dl.-8.0 mg./dl., respectively). Lower Ig-A in Group 3 patients compared to Group 2 were not statistically significant. Contrary to Ig-A figures, Ig-M did not differ in any of these groups of patients compared to the controls. In patients with pancreatic malignancy (Group 5), Ig-A ranged between 0.1 and 64 mg./dl. (median 0.1 mg./dl.) and Ig-M from 0.5-24 mg./dl. (median 2 mg./dl.). Although a marked depression of Ig-A and considerable elevation of Ig-M levels were observed in this group of patients, the differences were not found statistically significant, due to extremely deviated values compared with other groups. Interestingly enough those patients with localized tumors (three cases) had the higher Ig-A and lower Ig-M levels, whereas patients with liver-node metastases and disseminated carcinomatosis showed exactly the reverse pattern.

The ratios A/M as well as A/T showed more striking differences between the groups of patients studied (Fig. 1). In group 1 patients, the A/M ratio ranged between 1.75-48.0 with a median value of 6.20, whereas the A/T ratio was found between 0.220 and 0.584 with a median value of 0.330. These values were significantly lower than those in Group 2 (chronic pancreatitis) and significantly higher than

TABLE III

Calculated A/M and A/T Ratios for Control Patients and Patients with Pancreatic Disease

	Immunoglobulin A/M	Immunoglobulin A/total
Chronic pancreatitis	10.83	0.39
Pancreatic cancer	0.2	0.01
Normal control	5.5	0.33

those in Group 5 (pancreatic cancer) patients. The respective values of the cancer patients are shown in Table II.

The data in Table I clearly indicated that the A/M ratio in pancreatic cancer was statistically different from the ratio in the other groups. On the other hand the A/T immunoglobulin ratio was statistically different only for patients with chronic pancreatitis compared to the other groups. This ratio was not different within these latter groups.

COMMENT

While immunoglobulin A. represents a relatively small proportion of total serum immunoglobulins, secretory immunoglobulin A is the predominant gamma globulin of the external secretions.[5] Moreover, abnormal Ig-A secretion in the mucous membranes has been associated with benign and malignant gastrointestinal,[6-9] pulmonic,[10, 11] or urinary tract pathology.[12]

Theoretically, an intact immunosecretory system operates in the mucosal membranes and glandular tissues as a dynamic germicidal barrier.[13] Immunohistochemical and Ig-bearing lymphocyte migration studies have indicated that nonbacterial and nonviral stimuli may result in distinct changes in the secretory immunoglobulins exerting their function in the presence of an intact epithelium.[14]

The mechanism(s) underlying these changes in immunosecretory patterns of the diseased pancreas are obscure and only speculative explanations may be offered at the present time. In a previous report, Lendrum and Walker[15] were able to locate an organ-specific antigen in the microsomal fraction of pancreatic homogenates of patients with calcific pancreatitis. Whether the diseased pancreas elaborates antigenic material triggering a systemic immunological response or the response is elicited locally in pancreatic tissue are possibilities requiring further investigation. In independent studies on patients with chronic calcifying pancreatitis, Bank[16] found increased levels of serum Ig-A and Ig-G, whereas Ig-M was unaffected. Dani, et al[17] reported higher serum Ig-A and Ig-M in the same type of patients. There is, indeed, a voluminous work suggesting alterations in serum immunoglobulin levels in patients with either benign or malignant diseases.[1] We have previously reported that such changes in serum immunoglobulin levels in myasthenic women may indicate increased cancer risk especially if determined as ratios of A/M and A/T.[18] Since, however, selective glandular transfer and local immunoglobulin production are unique characteristics of the secretory system of glandular organs, studies of the secretory patterns of the PDF should be more revealing in screening pancreatic pathology than serum findings. In fact, Clemente, et al[19] reported increased spillage of albumin and serum immunoglobulins in the pancreatic juice of patients with chronic calcifying pancreatitis. Our data support this finding.

Assuming minimal contamination of secretory fluid by diffusable serum immunoglobulins, and accepting the quantitative distribution of immunoglobulin-containing cells in the upper gastrointestinal tract to be predominant for gamma A globulin,[14] it is conceivable that the PDF changes in immunoglobulin patterns observed in chronic pancreatitis and pancreatic cancer are reflections of a locally occurring immunologic response to pancreas-originating antigens. In fact, in early pancreatic cancer a marked increase in Ig-A and Ig-M and in late pancreatic cancer a disappearance of Ig-A was observed. Similar alterations in secretory immunoglobulin A patterns can be observed in the data of Weisz-Corrington, et al[20] for colonic cancer. Also concordant with our findings is the study of Crabbé and Herman[21] who found an altered distribution of Ig-A and Ig-M containing lymphocytes in the stomach mucosa, i.e. in peptic ulcer of the lesser curvature, an increase in Ig-A and Ig-M-bearing cells with more prominent "M" secreting cells compared to the normal stomach. The calculated ratio of A/M bearing cells in this study was decreased from 8.8 in normals to 2.01 for gastric ulceration but it was markedly increased (to 27.25) in exudative gastropathy. In gastric cancer patients, however, there was a marked decrease in "A" cells accompanied by a marked increase in "M" cells; the ratio A/M decreased to 0.72. Similar patterns of gastric fluid Ig-A hypersecretion in localized or benign tumors were also found by Levy, et al,[8] whereas in advanced gastric cancer they reported considerably decreased gastric Ig-A levels. Although ratios of A/M or A/T were not calculated, perusal of the data indicates that a reversed ratio with "A" as numerator was present.

In our series, the calculated A/M and A/T ratios are listed in Table III for controls, patients with chronic pancreatitis and patients with pancreatic cancer. It is clear that the ratios for inflammation and cancer differ significantly from each other and from the nonpancreatitis group. The increased ratios in patients with pancreatic inflammation result mainly from increases in Ig-A. The decreased ratios in pancreatic cancer derive from a fall in Ig-A associated with a rise in Ig-M. It must be stressed, however, that the immunoglobulin secretory findings in early localized pancreatic cancer resemble those of inflammation suggesting that the immunologic responses are similar. As the cancer grows and spreads, Ig-A is suppressed or disappears, so that the immunological pattern becomes different. The data would also indicate that a local operational Ig-A-Ig-M switch may be operative in pancreatic cancer but is not observed in benign pancreatic inflammation.

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Communication from Abroad

Oral Administration of Chymotrypsin Labile Peptide for a New Test of Exocrine Pancreatic Function (PFT) in Comparison with Pancreozymin-secretin Test

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A new test using N-benzoyl-L-tyrosyl-p-aminobenzoic acid(N-BT-PABA) for an evaluation of exocrine pancreatic function was compared with a pancreozymin-secretin test in 38 subjects. Urinary recovery of PABA, which is absorbed from the intestine and conjugated in the liver after an oral administration of N-BT-PABA, depends mainly on chymotrypsin activity. The recovery rate of PABA in urine decreases in chronic pancreatitis, in which chymotrypsin activity in the duodenal juice is disturbed. The recovery rate of PABA in calcifying chronic pancreatitis was 40.2 ± 15% and significantly less than 81.2 ± 7.4% in normal subjects ($P < 0.01$). The amount of PABA in urine during eight hours was correlated with parameters of volume output, bicarbonate concentration and amylase output stimulated by injections of pancreozymin and secretin (P-S test). The new test using N-BT-PABA is useful for the evaluation of exocrine pancreatic function in general practice.

INTRODUCTION

The pancreozymin-secretin test (P-S test) is valuable for evaluation of exocrine pancreatic function.[1, 2] But since this test is not readily available for practitioners and causes much discomfort to patients, another simple test for an evaluation of exocrine pancreatic function would be clinically valuable. Imondi, et al[3] reported that a new test which used N-benzoyl-L-tyrosyl-p-aminobenzoic acid (N-BT-PABA) was useful. N-BT-PABA, orally administered, is split into free PABA in the presence of chymotrypsin. The PABA is rapidly absorbed from the intestine, conjugated in the liver and excreted into urine. The recovery of PABA in urine is used as an index of exocrine pancreatic function since chymotrypsin activity depends upon exocrine pancreas function.

In the present study, we investigated the value of the N-BT-PABA test in a diagnosis of pancreatic disease. In 38 subjects, the urinary excretion of PABA was compared with parameters of volume output, maximal bicarbonate concentration and amylase output in duodenal juice by the P-S test.

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SUBJECTS AND METHODS

Fourteen healthy male volunteers, aged 20 to 37 years, were used as normal controls. Sixteen patients with chronic pancreatitis were selected for this study. Criteria for a diagnosis of chronic pancreatitis were: 1. the presence of recurrent abdominal pain, chronic alcoholism and glucose intolerance and 2. evidences of exocrine pancreatic dysfunction as evaluated by the P-S test. In the case of O. T. (Table I) a patient with no history of abdominal pain chronic pancreatitis was diagnosed not only by the P-S test but by a roentgenogram showing a dilation of main pancreatic duct beyond 12 mm. in diameter. In four patients with recurrent abdominal pain, hyperamylasemia and chronic alcoholism, chronic pancreatitis was diagnosed on clinical grounds. Thirteen diabetic patients were studied. They had no history of abdominal pain. Seven patients were treated with insulin, the other managed by diet alone. Eleven patients with other disorders of the gastrointestinal tract were examined, viz. duodenal diverticulum in three patients, gastritis atrophicans in five, and cholelithiasis in three.

Simple pancreatic function test (PFT):—All subjects were examined after an overnight fast. A tablet of 0.5 gm. of N-BT-PABA containing 169 mg. of PABA was orally administered. The concentration of aromatic amines in urine was determined by the method of Bratton-Marshall[4] with modifications according to Smith, et al.[5] Urinary aromatic amines were usually negligible unless the patient was taking drugs containing para-aminobenzoyl derivatives. Results were expressed as per cent recovery of PABA in urine and calculated as follows:

$$\% \text{ recovery} = \frac{\text{Total aromatic amines (mg.)}}{169 \text{ mg. of PABA}} \times 100$$

Pancreozymin-secretin test:—After an overnight fast, a Dreiling double tube was positioned with its tip in the fourth portion of the duodenum under fluoroscopic control. The gastric and duodenal juices were aspirated continuously with separated suction pumps. Basal secretion of the duodenal juice, consisting of pancreatic juice and bile, was collected for 20 minutes before stimulations by pancreozymin and secretin. After a single intravenous injection of pancreozymin (Boots, 1 U./kg.) the duodenal juice was aspirated for 20 min. Immediately secretin (Boots, 1 U./kg.) was injected intravenously. The duodenal juice was collected for one hour, in periods of 10, 10, 20 and 20 minutes after the injection.

Total volume of the duodenal juice aspirated during 60 minutes after the secretin injection was expressed as ml./kg./hr. Maximal bicarbonate concentration in the duodenal juice was determined by the gasometric method of Natelson[6] and expressed as mEq./l. Amylase activity of the duodenal juice was measured by the method of Caraway.[7] Total amylase output was expressed as U./kg. during 80 minutes after injections of pancreozymin and secretin.

In normal subjects the volume output, the maximal bicarbonate concentration and total amylase output were more than 1.64 ml./kg./hr., 84.3 mEq./l. and 1,200 U./kg., respectively. The PFT and the P-S test were performed in 38 subjects within an interval of one month. For comparison of results in different groups Student's "t" test[8] was performed. Comparison of PFT with the volume output, the maximal bicar-

TABLE I

RESULTS OF PFT AND P-S TESTS

Name	Age (yr.)	Sex	8-hr. urinary excretion of P.A.B.A. (%)	Pancreozymin-secretin test			Other
				Volume	Bicarbonate	Amylase	
Control							
H.M.	37	M	69				
S.A.	34	M	82				
T.S.	32	M	85				
T.S.	31	M	94				
Y. S.	29	M	84				
H.S.	28	M	88				
Y.M.	26	M	93				
T.H.	25	M	84				
K.N.	23	M	79	3.34	99	3,601	
T.I.	23	M	76	4.59	97	3,511	
S.S.	20	M	75	1.98	102	2,103	
T.N.	20	M	75	1.98	94	1,615	
K.Y.	20	M	78				
M.N.	20	M	80				
Chronic pancreatitis suspiciously							
M.N.	30	F	86	3.65	86	3,257	Provocation:positive
Y.N.	52	M	85	3.60	85	2,610	
S.S.	51	M	72	5.02	125	4,492	Heavy alcoholism
T.N.	39	M	66	2.71	110	2,015	Heavy alcoholism
Noncalcifying pancreatitis							
T.Y.	42	M	66	1.55	38	208	Alcoholism, D.M.
T.K.	43	M	40	1.76	14	943	Alcoholism, D.M., diarrhea
A.K.	42	M	79	3.90	62	371	Alcoholism
T.T.	35	M	63	2.32	60	959	D.M.
O.T.	68	M	65	1.56	56	1,392	Painless pancreatitis
Calcifying pancreatitis							
T.S.	42	M	22	1.20	45	57	D.M. (Insulin)
T.S.	45	M	44	1.06	42	471	D.M. (Diet)
A.M.	47	M	46	1.66	31	185	D.M. (Insulin)
E.M.	36	F	21	0.60	20	200	D.M. (Insulin)
M.S.	42	M	58	2.22	85	1,456	
T.S.	43	M	57	1.84	50	420	D.M. (Diet)
S.F.	48	M	34				

TABLE I *(continued)*

RESULTS OF PFT AND P-S TESTS

Name	Age (yr.)	Sex	8-hr. urinary excretion of P.A.B.A. (%)	Pancreozymin-secretin test			Other
				Volume	Bicarbonate	Amylase	
Primary diabetes mellitus							
S.S.	49	M	88	2.36	109	1,933	Diet
M.F.	49	M	70	3.14	83	1,939	Diet
K.N.	38	M	83	5.44	91	4,975	Diet
T.S.	22	M	62	1.57	97	2,049	Rapitard 36 U.
T.N.	42	M	81	3.07	98	3,040	Diet
T.T.	68	F	64	1.62	74	1,934	Lente 24 U.
F.S.	38	F	74	2.46	92	2,413	Rapitard 28 U.
K.O.	28	F	52	2.84	120	2,483	Lente 18 U., diarrhea
C.K.	64	M	59	2.25	91	1,334	Diet:provocation:positive
K.M.	52	F	83	2.62	92	3,071	Diet
T.S.	38	M	88				Diet
T.N.	42	F	87				Rapitard 34 U.
T.K.	25	F	82				Lente 20 U.
Duodenal diverticulum							
L.I.	75	M	95	1.85	82	1,822	
Y.O.	35	F	88	1.83	97	3,809	
T.I.	56	F	84	2.98	95	2,666	
Gastritis atrophicans							
T.K.	35	M	94	3.82	115	5,164	
L.T.	25	F	58	3.57	107	2,622	Provocation:positive
T.O.	38	M	84	2.96	92	3,496	
F.K.	42	F	86				
M.A.	38	F	89				
Cholelithiasis							
T.T.	49	F	84	3.01	113	3,356	
M.M.	39	F	90	3.16	96	2,902	
K.K.	50	F	76	4.99	94	4,194	

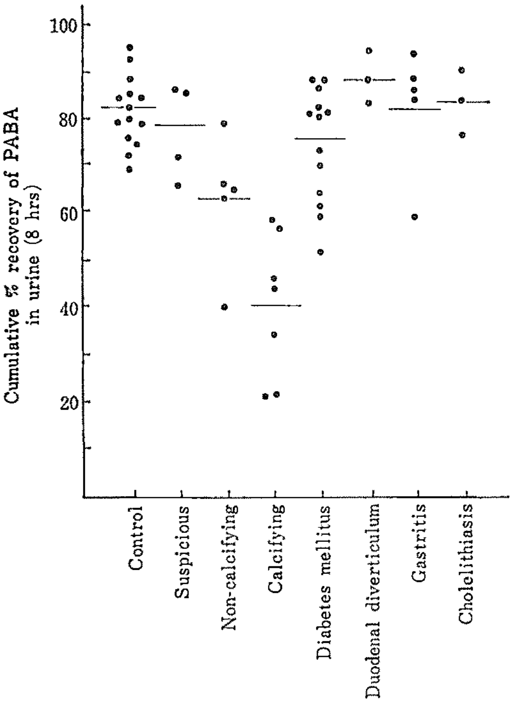

Fig. 1—Cumulative eight-hour PABA recovery (Mean ± S.D.) in the various groups.

bonate concentration and the amylase was calculated through an Okitac 50-computer program by a polynominal regression.

RESULTS

The recovery rate of PABA during eight hours after an oral administration of N-BT-PABA is shown in Table I and Figure 1. The recovery rate of PABA in the controls was 81.2 ± 7.4% (Mean ± 1 S.D.). In calcifying chronic pancreatitis and non-calcifying chronic pancreatitis, the value was 40.2 ± 15% and 62.0 ± 14.1%, respectively, which value is significantly less than that of the control group ($P < 0.01$). The recovery rates of PABA in suspected chronic pancreatitis, diabetes mellitus, duodenal diverticulum, gastritis atrophicans and cholelithiasis were 77.2 ± 9.8%, 77.4 ± 12.2%, 81.0 ± 5.5%, 82.0 ± 13.9% and 83.3 ± 7.0%, respectively. These values were statistically insignificant versus that of the control group.

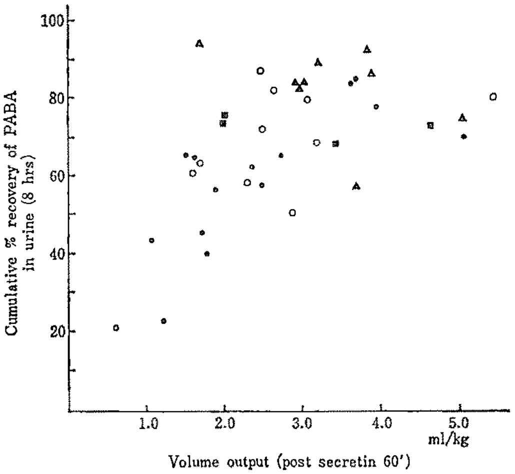

Fig. 2—Comparison of eight-hour urinary PABA excretion with volume output in duodenal aspirates in four controls (■), 15 chronic pancreatitis(●), 10 primary diabetes mellitus(O), nine other gastrointestinal disease(▲). A significant correlation between urinary PABA excretion and volume output ($r = 0.5932$, $P < 0.01$).

The per cent recovery of PABA in 38 subjects was correlated with the volume output ($r = 0.532$, $P < 0.01$), the maximal bicarbonate concentration ($r = 0.626$, $P < 0.001$) and the amylase output ($r = 0.6784$, $P < 0.01$). These correlations are shown in Figures 2, 3 and 4, respectively. From these results, the per cent recovery of PABA was shown to decrease in the patients with exocrine pancreatic dysfunction as evaluated by the P-S test.

COMMENT

The pancreozymin-secretin test is considered to be an accurate and reliable method for the evaluation of exocrine pancreatic function.[2] The P-S test, however, is not available in all institutions. If urinary recovery rate of PABA after an oral administration of N-BT-PABA accurately reflects an impaired exocrine pancreatic function, the test using N-BT-PABA is useful

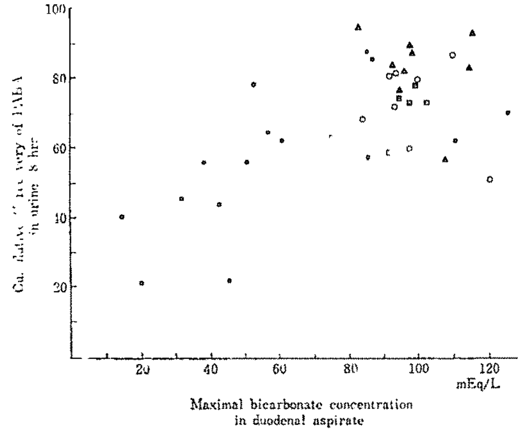

Fig. 3—Comparison of eight-hour urinary PABA excretion with maximal bicarbonate concentration. A significant correlation is shown ($r = 0.6260$, $P < 0.01$).

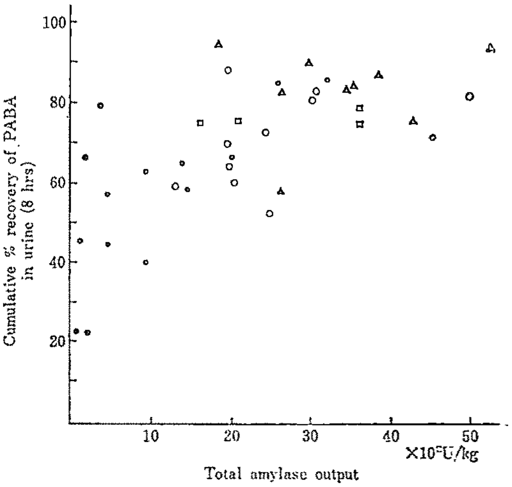

Fig. 4—Comparison of eight hour urinary PABA excretion with total amylase output. A significant correlation is shown ($r = 0.6784$, $P < 0.01$).

in the diagnosis of chronic pancreatitis. Imondi, et al[3] reported that in experimental pancreatic insufficiency which was induced by ligation of the pancreatic duct in rats, swine and dogs, urinary recovery rate of PABA decreased. The total recovery rate of PABA after an oral administration of N-BT-PABA in man was correlated with Lundth's test.[9]

In the present study, an attempt was made to compare the urinary excretion of PABA with the P-S test. The data demonstrated that the recovery rate of PABA was significantly correlated with parameters of the P-S test. The total eight-hour per cent recovery of PABA was below 60% in the calcifying chronic pancreatitis and below 70% in the noncalifying pancreatitis except for the case of A. K. as shown in Table I and Figure 1. These data indicate that the recovery rate of PABA in urine reflected exocrine pancreatic dysfunction and are in agreement with the results of Greenberger[10] who reported that the recovery rate of PABA was correlated with the maximal bicarbonate concentration and the trypsin activity in the duodenal juice stimulated by pancreozymin and secretin.

Conversion of N-BT-PABA to PABA depends mainly on chymotrypsin activity. Excretion of PABA into urine after absorption from the intestine and conjugation in the liver may be disturbed due to renal dysfunction and to liver disorder. This possibility, however, was denied by the results of Gyr, et al,[9] who showed that chronic liver disease and impaired renal function did not interfere with the excretion of PABA. Yet, in the case of K. O. a diabetic with diarrhea, the recovery rate of PABA was decreased in spite of normal exocrine pancreatic function as evaluated by the P-S test. In patients without diarrhea, the recovery rate of PABA coincides with the exocrine pancreatic function in diabetes mellitus. Since the exocrine pancreas may be disturbed in insulin-dependent diabetics,[11] the PFT could be useful for evaluation of the exocrine pancreatic function.

CONCLUSIONS

Our results showed that the new test (PFT) of exocrine pancreatic function using oral administration of N-BT-PABA appears suitable for screening for pancreatic insufficiency in general practice.

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Computed Tomography and Abdominal Diseases*

A Valuable Diagnostic Aid?

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Computed tomography (CT) has simplified the evaluation and treatment of many patients with intraabdominal and retroperitoneal diseases. The applications of CT have been discussed in several publications and presentations.

This test is based on the amount of attenuation that a roentgen ray undergoes while passing through body tissues. All scanning is done through an arc of 180° in a period of 13 seconds to 2.25 minutes (depending upon the scanner used). The image is recorded in black and white, color and on digital print-out. In addition to visual display, attenuation numbers are available to disclose whether a mass is solid or cystic.

Many unanswered questions have been raised about CT. The number of false positive and false negative scans and the incidence of observer errors is presently unknown. As important, is the question of whether CT is better, cheaper, or a more accurate way to diagnose intraabdominal diseases than other more conventional roentgenographic tests.

CT of the abdomen has been found applicable in evaluation of disease of the gallbladder, pancreas and liver. In a preliminary study of eight patients with biliary tract disease CT was helpful in detecting cystic or common duct obstruction in five patients. This suggested that CT might help diagnose gallstones, as their density differs from the surrounding bile in the gallbladder. Since then we have compared echograms, CT and cholecystograms in 35 patients with suspected gallbladder disease (Fig. 1). Although the data are preliminary and unpublished, our findings suggest the CT or echography will supplement but not replace cholecystography as a routine diagnostic test.

Earlier studies[1, 2] demonstrated that the pancreas could be visualized easily with CT and loss of the peripancreatic fat plane or enlargement of the head could be demonstrated in cross sectional view (Fig. 2).

Eighty-two patients with carcinoma or pancreatitis were evaluated by CT and when possible CT was compared with angiography to determine the value of each test.[2] Of 40 normal patients (proven by clinical course or surgery) five had false positive CT scans. In three patients this was based on loss of the peripancreatic fat plane (a now unreliable sign particularly in thin people). In two others, fluid filled the stomach or intestine, incorrectly suggesting a pancreatic abnormality.

Seventeen patients ultimately diagnosed as having adenocarcinoma were

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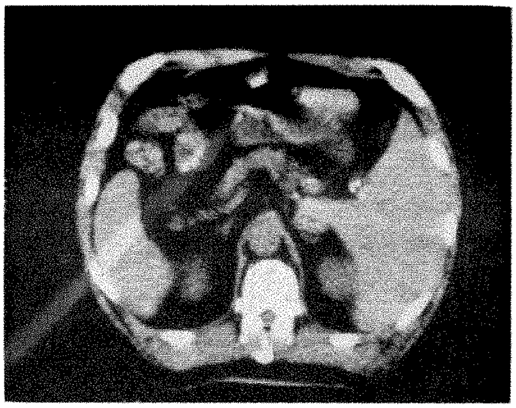

Fig. 1—Normal pancreas and biliary stone.

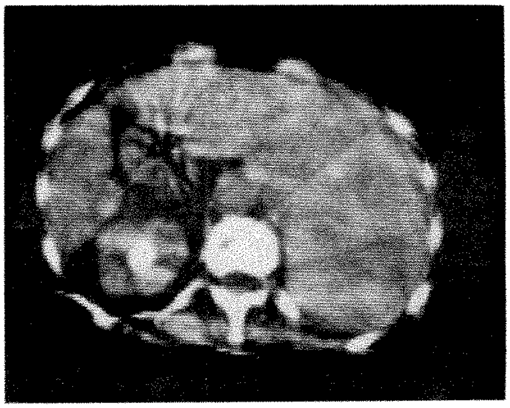

Fig. 3—Hepatic tumor.

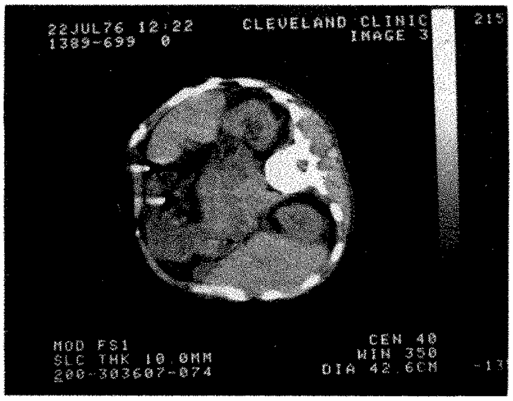

Fig. 2—Tumor of the pancreas.

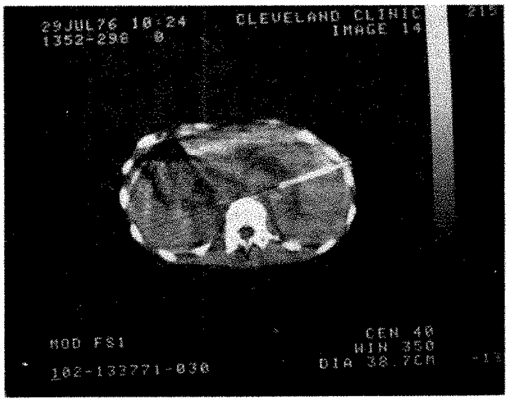

Fig. 4—Dilated biliary percutaneous drainage.

evaluated. CT was positive in 13, negative in one (a pseudocyst was diagnosed but a proximal carcinoma missed) and in three motion or artifact limited the diagnosis. In seven an angiogram was done: it was positive in five and negative in 12.

When pancreatitis caused enlargement of the gland or calcific changes, CT was of value but limited when these changes were not present.

LIVER

Earlier experience with angiography showed the limitations of two-dimensional studies of some lesions that approximated the interlobar fissure were better defined by CT.

Six patients who had CT and nuclear scans were studied (an additional 15 had only CT scans).[3] Only a few positives were diagnosed. Seventeen of 22 hepatic tumors were correctly diagnosed by each method (Fig. 3). Of the five lesions missed, their density was similar to surrounding parenchyma. The use of contrast agents that concentrate in normal liver has further improved this diagnostic accuracy. In cirrhosis, CT proved diagnostic in eight of 11, whereas nuclear medicine was more accurate in 10 of 11 patients. This is because of the reversal of isotope uptake between spleen and liver. This has been done with CT and the diagnostic accuracy has now increased. An additional advantage of CT in liver disease has been to drain or biopsy intrahepatic lesions (Fig. 4). One further addition has been to decompress percutaneously obstructed bile duct with CT. In four patients with unresectable high bile duct tumors good palliation has been obtained.

.Three questions were raised at the beginning of this presentation.

1. What is the incidence of false positive and false negative studies? Our estimate based on these early studies of 3,000 patients is a range of 5% to 10%.

2. This number will change with the development of technical improvements in CT scanners and as experience in interpretation improves. Paradoxically our experience may be the opposite.

3. As an increasing number of radiologists read CT scans, I believe the number of inaccuracies has increased during this period and a few negative operations have been performed based on these interpretations. I state this as a word of caution to those beginning to interpret CT scans.

Finally, the priority of CT scanning in evaluating biliary hepatic and pancreatic diseases remains to be determined. While these early studies showed no advantage of CT over nuclear scanning or angiography, its noninvasiveness, short exposure time, high degree of patient acceptance, and potential for direct biopsy make it a more popular test at our hospital. Further studies including cost analyses are necessary.

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Recurrent Renal Carcinoma Causing Intestinal Hemorrhage

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Three cases of gastrointestinal bleeding caused by secondary renal carcinoma are presented. Hemorrhage occurred secondary to invasion of bowel anatomically related to the primary tumor. Bleeding can best be controlled by excision of tumor and involved intestine. Surgery is justified by the unpredictable prognosis for renal carcinoma with secondary disease.

Renal carcinoma classically presents with the triad of hematuria, pain and tumor. Extrarenal extension may be responsible, however, for the dominant clinical picture. Lawson, et al[1] described a case of duodenal hemorrhage secondary to submucosal implantation of tumor metastatic from a left renal carcinoma. Franciosi and Russo's[2] patient, 13 years after nephrectomy for renal cell carcinoma, presented with obstructive jaundice secondary to delayed involvement of the head of the pancreas. Starr and Miller[3] found submucosal implantation of a solitary jejunal metastasis 20 years after removal of a renal cell carcinoma. Intra-abdominal[4] and retroperitoneal[5] hemorrhage have also been described as clinical presentations and are probably related to the vascular and friable nature of renal cell tumor masses. Systemic manifestations include polycythemia, fever of unknown etiology, hypercalcemia and abnormal hepatic function,[6] all with localized renal tumors. Recently, Rubins and Wakem[7] described hypoglycemia and a lukemoid reaction associated with invasive hypernephroma.

The course of extrarenal disease after removal of the primary tumor and limited secondary disease is unpredictable in length and progression. The regression of metastatic pulmonary[8] and intracranial[3] lesions after the removal of the primary tumor has been documented. The first case below represents a long-term survivor with secondary disease presenting as late colonic bleeding.

Case 1:—T. M., a 40-year old white woman, was admitted on 16 September 1958, with two episodes of bright red bowel movements preceded by left upper quadrant discomfort. In 1955, a left nephrectomy had been performed for a renal carcinoma involving the lower pole. The tumor penetrated the renal capsule and was adherent to related peritoneum. No vascular invasion was seen. History included inactive pulmonary tuberculosis. On admission the only positive physical finding was a nontender, soft, left upper quadrant mass. Sigmoidoscopy to 24 cm. was nondiagnostic. Barium enema demonstrated a round filling defect, 5 cm. in diameter, in the lower descending colon and proximal stenosis. Chest x-rays and a bone survey did not show metastases. Abdominal exploration, performed through a left flank incision, revealed a normal liver and a large, vascular retroperitoneal tumor mass extending behind the descending colon from splenic flexure to sigmoid colon. Left hemicolectomy and hemiomentectomy with *en bloc*

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resection of retroperitoneal tumor and portions of iliopsoas and *quadratus lumborum* muscles were performed. Surgical pathology described an 18 × 10 × 6 cm. nodular, hemorrhagic tumor mass with 16 cm. of colon containing a metastatic polyp 4 cm. in diameter. Histology was similar to the original left renal carcinoma. Part of the polyp was necrotic and the mucosa overlying numerous thin-walled inflammatory blood vessels was ulcerated. Regional lymph nodes and resected muscle were free of tumor but involved in an inflammatory process. After hospital discharge on the 30th postoperative day, barium enema demonstrated a healed anastomosis. Postoperative radiotherapy, 4,000 rad, was given through anterior and posterior portals covering para-aortic nodes and the left abdomen. In 1960, a 2 cm. encapsulated mass of renal cell carcinoma in the left pectoralis major muscle was excised. Skull and chest x-rays were normal. Three thousand rad of cobalt therapy were delivered to the left axilla. In 1962, chest x-rays revealed two pulmonary metastases, one near the left hilum and one at the right base, each about 2 cm. in diameter. In 1963 a chest x-ray demonstrated that the pulmonary lesions had enlarged. In 1964, prompted by rapid enlargement, the left pulmonary mass, now 6 cm. in diameter and localized to the lower lobe, was excised by wedge resection. The right tumor mass was 3 cm. in diameter and there was no evidence of other systemic disease. A wedge resection of the right lower lobe was performed. In 1966, 11 years postnephrectomy and eight years after removal of the first manifestation of recurrent tumor as colonic bleeding, multiple cerebral and vertebral metastases were demonstrated, and she soon expired.

Comment:—Contiguous pathology between kidney and alimentary tract was discussed by Arthur and Morris.[9] With trauma and inflammatory processes including parasites, tuberculosis, nephrolithiasis and pyelonephritis, fistulas develop between the renal collecting system and bowel lumen. These occur along the alimentary tract from stomach to rectum. Arthur and Morris state that malignant connection between kidney and gut is probably preceded by an inflammatory fistula. They describe a tumor fistula containing squamous cell carcinoma. Renal-enteric connections can also occur as solid structures in which case the clinical manifestation is different and unrelated to the passage of urine into the gastrointestinal tract. Kaufman's[10] collective review of concurrent lesions of colon and kidney defined the main etiologic categories as traumatic and inflammatory. Rarely neoplasm is the cause and "the colon is nearly always the organ in which cancer affecting both originates." The three cases presented here represent renal tumor invasion of juxtaposed intestine which is reflected by bleeding. An inflammatory process may also accompany the tumor and hence either neoplastic or primary inflammatory disease may be associated with fever.

Case 2:—M. P. M., a 56-year old woman, was admitted 30 December 1961, with a four-day history of epigastric cramps and loose tarry stools and weight loss for three months. She used aspirin for arthritis. Six months previously, a right nephrectomy had been performed for renal cell carcinoma. An 8 cm. clear cell tumor of the lower pole of the right kidney, which had not penetrated the capsule, had invaded the main renal vein. Admission examination revealed pallor and no fever. Blood pressure was 130/90 and pulse 112. There was moderate epigastric tenderness. Hematocrit was 17%; hemoglobin, 6.5 gm.%. A chest x-ray showed bilateral metastatic disease. Because of continued bleeding she received 2,500 cc. of whole blood. Liver tests, coagulation studies and electrolytes were normal. Bleeding ceased; temperature was

38.5-39.5° C; hemoglobin, 11.4 mg.% and white blood count, 17,550/cu. mm., associated with epigastric pain and cramps. Sigmoidoscopy was normal. Barium enema showed some diverticula of the sigmoid colon and possibly several oval-shaped filling defects in the cecum. A stool culture grew out *Staphylococcus aureus* (coagulase positive), and Oxycillin was begun. Colonic bleeding with hypotension recurred requiring 2,000 cc. more whole blood. Operation was recommended with Case 1 in mind, which at this time had survived for three years postoperatively. On 27 January laparotomy revealed extensive tumor in the right renal bed extending into the adjacent colon. Cecal and retroperitoneal tumor were resected *en bloc*. The ileocecal valve was distorted by hemorrhagic tumor. Histologically this secondary renal carcinoma invaded from retroperitoneum through muscularis to the overlying mucosa. The postoperative course was smooth and the patient was discharged. But she soon expired at home due to rapidly advancing pulmonary metastases.

Comment:—Involvement of the right colon by recurrent tumor six months postnephrectomy here presents a confusing picture of gastrointestinal bleeding and fever suggesting both peptic ulcer disease and enterocolitis. The presence of diverticula, common in the age group of patients with renal carcinoma, may also confuse the clinical impression. The hemorrhagic problem may be expeditiously controlled by surgical extirpation of involved tumor and intestine.

Case 3:—J. D., a 64 year old white man was admitted on 5 May 1969, with syncope. Right nephrectomy had been performed for hypernephroma in 1961. He was well until six months previously when intestinal bleeding required laparotomy which revealed unresectable metastatic tumor obstructing the duodenum. Gastroenterostomy and vagotomy were performed elsewhere. On this admission he complained of weakness, dizziness, anorexia and 4.5 kg. weight loss in four months with no abdominal pain or vomiting. Positive findings included temperature of 38° C and a large, multinodular, right upper abdominal mass. Hematocrit was 23%; hemoglobin, 7.4 gm.%; BUN, 65 mg.%. Continued bleeding required 2,500 cc. whole blood transfusion and prompted laparotomy. Clear cell carcinoma had invaded the duodenal sweep, the head of the pancreas, the stump of the right renal artery and the celiac axis. The lumen of the duodenum contained a friable fungating tumor mass, actively hemorrhaging and invading across the posterior and medial duodenal wall. Ligature of the pancreaticoduodenal arcade controlled hemorrhage. Hemigastrectomy, duodenectomy, choledochojejunostomy and pancreatic duct ligation were done. A 6 cm. mass of free tumor was extracted from the jejunum. Five thousand cubic centimeters of whole blood transfusion were required during surgery. Postoperatively he initially improved but ultimately succumbed to gram negative pneumonia in the third postoperative week.

Comment:—The third case exemplifies a delayed recurrence manifest as recurrent duodenal hemorrhage. The friable nature of renal cell carcinoma and invasion of the pancreaticoduodenal arcade was demonstrated as the cause of hemorrhage. Free tumor, capable of obstruction, was extracted from the jejunum. The patient expired three weeks after surgery. Had gram negative sepsis not occurred, longer palliation might have been obtained.

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Entrapment of Snare Loop During Polypectomy

A RECURRING PROBLEM

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Electrosurgical removal of gastrointestinal polyps through the modern fiberoptic endoscopes has become an established procedure. The associated morbidity and mortality is generally appreciated as also is the fact that its incidence varies inversely with the degree of skill and experience of the endoscopist. In addition, however, the occurrence of complications is predicated upon the anatomic characteristics and location of the lesion to be resected and also upon the capabilities and safety of the instruments and of the electrosurgical appliances which are employed. The former factor must be coped with, since it is not available to alteration. The latter, however, can be modified; defects or deficiencies which are experienced during their use may be expounded and may be corrected.

We are reporting a complication encountered during electrosurgical removal of a polyp from the sigmoid colon, using a noose-type wire snare.

REPORT OF CASE

A 68-year old white male, with compensated arteriosclerotic heart disease, underwent colonoscopy because of the demonstration of a polyp in the sigmoid colon by barium enema examination and because a small (0.7 mm.) rectal polyp was discovered during sigmoidoscopy. The 180 cm. ACMI Double-channel Colonoscope (Model #F9A), wire snare-cautery, and electrosurgical unit (Pneumotome®) were used for the procedure.

After overcoming resistance in the sigmoid colon which necessitated using the "alpha maneuver", total colonoscopy to the cecum was achieved with ease and was documented radiographically by a film obtained with a portable unit.

During withdrawal of the instrument, the mucosa presented a normal appearance throughout the extent of the colon. In the region of the mid sigmoid, at approximately 40-45 cm. from the anal margin, a bilobed, pedunculated polyp was encountered. It was estimated to measure 1.5 cm. in diameter and corresponded, in location, to the one which had been demonstrated by barium-contrast radiography (Fig. 1). The polyp was located in an awkward position, lying just beyond and above, a prominent and persistent, sickle-shaped mucosal fold. The patient was rotated into various positions in order to find the one which provided the best exposure for approaching the lesion. In spite of this, however, only a portion of the polyp could be seen, presenting, as the rising sun over the horizon, a hemispherical mass behind the fold previously described.

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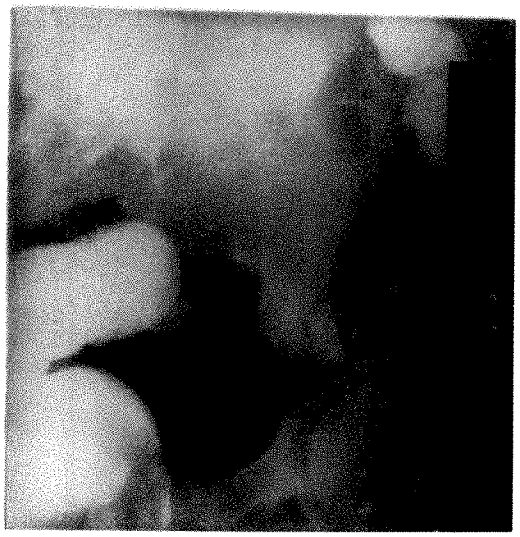

Fig. 1–Barium enema demonstrating polyp in the sigmoid colon.

Moderate difficulty was encountered in maneuvering the loop of the wire snare into position to obtain the polyp. The loop was apposed to its presenting aspect and then was drawn over the hidden portion of the mass by forcefully flexing the tip of the colonoscope against the fold which obstructed full view of the lesion. This succeeded in producing a "red-out", totally obscuring the field of vision and the fact that the polyp indeed had been obtained had to be established "blindly" by the sense of feel transmitted by the handle of the snare as the loop was gently closed. It then became possible to drag the entire polyp into view by flexing the tip of the colonoscope with the protruding snare in the opposite direction. This revealed that only half of the bilobed polyp had been ensnared. Rather than attempt to reposition the wire loop to place it closer to the pedicle, it was elected to resect the snared portion. This was readily accomplished and the excised segment was permitted to drop free into the lumen in anticipation of resection of the remainder of the polyp, when both segments could be retrieved.

It was possible, once again, to ensnare the lesion "blindly" as before. Unfortunately, in the process, the colonoscope slipped away, distally from the lesion, a distance of several centimeters. We now were confronted by the predicament of having the snare secured to the polyp but being unable to visualize the area. Much time and patience was expended in attempting to advance the tip of the colonoscope, using the snare sheath as a guide to bring the polyp into view in order that it might be transected. This proved to be impossible. A similar impasse was experienced in attempts to disengage the snare loop from the polyp; pushing or pulling on the snare with the loop fully opened served only to displace the polyp and to exert a pull on the wall of the colon, occasioning complaints by the patient of pain and nausea.

We were reluctant to attempt to sever the lesion blindly with the electrosurgical current. Instead, it was elected to extract the colonoscope from the patient, over the snare, leaving the latter in place. This was accomplished and the loop of the snare now remained trapped around the polyp (Fig. 2), while its proximal end and operating handle protruded from the channel of the colonoscope which now lay entirely outside of the patient. Traction was again exerted on the snare with the loop fully opened but it did not release from the polyp. Since the tedious efforts described required the insufflation of a large quantity of air into the patient's colon, causing him discomfort, a rectal tube was introduced and left in position for a period of 15 minutes. This permitted escape of the accumulated air and concomitant deflation of the patient's abdomen.

The 105 cm. ACMI Colonoscope (Model F0 9000 PL) was then introduced into the rectum and, under direct view, was advanced, parallel to the snare. Once

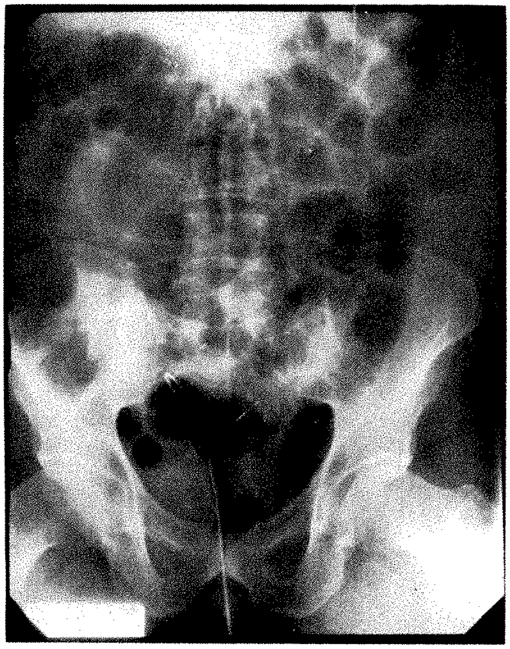

Fig. 2—Flat plate abdomen demonstrating entrapment of the snare around the polyp pedicle (colonoscope removed).

again, impedence was encountered in the sigmoid colon, just below the polyp. This time the "alpha maneuver" alone did not succeed to overcome the problem and 0.5 mg. of Glucagon was required to be administered intravenously as well. The colonoscope then could be advanced easily and, after traversing just a few centimeters, the level of the polyp was reached. Mild traction was now exerted on the wire snare and its loop was visualized, establishing that it did indeed encircle the pedicle of the remaining portion of the polyp. The segment of colon was then distended with CO_2, the loop of the snare tightened and the pedicle of the polyp was transected successfully under direct view by application of electrosurgical current. The snare, now freed, was withdrawn and removed from the patient. The specimen was secured by suction to the tip of the colonoscope and retrieved by withdrawing the instrument. The colonoscope was then introduced again and was advanced to the splenic flexure in an effort to retrieve the first segment of polyp which had been excised. Despite, however, a very careful search, this could not be found in the colon, or in the contents of the bottle containing the suction fluid. Microscopic examination of the polyp and pedicle demonstrated the lesion to be a benign adenoma.

COMMENT

The experience which has been described, in which, following successful placement of a wire-loop snare over a pedunculated polyp, it becomes impossible to disengage the snare when the necessity arises, is a periodically recurring one. It poses a distinct hazard to the patient, causes him unnecessary discomfort, prolongs the procedure of polypectomy and is distressing to the endoscopist. A similar occurrence has been reported in which surgical operation was required in order to release a noose-type snare from a polyp in the cecum, about which it had become entrapped.[1] In that case, the polyp pedicle could not be transected by the electrosurgical current which was applied. It was surmised that the failure derived from the thickness of the pedicle and that the wire had become fused to it as a result of the heat generated during application of the electrosurgical current.

In the present case, the tip of the colonoscope accidentally became displaced distally from the ensnared polyp and subsequently could not be advanced into position again to visualize it. Since the lesion could not be seen, an electrosurgical current was not applied. Unfortunately, it was impossible to disengage the snare from the lesion, complicating and prolonging the polypectomy procedure. Similar entrapment has been experienced during polypectomy in other instances. In these cases, however, it was possible, with varying degrees of difficulty, to remove the snare from the polyps when, for various reasons, it became necessary to do so and to reposition it.

Electrosurgical accessories must be endowed with a fail-safe design, permitting their easy removal from a lesion when desired. This feature is lacking at times in the nonrotating, noose-type snare-cautery device but is inherent in the home-made ones. In these, the snare loop is formed by a continuous wire which enters and exits from the proximal end of the insulating sheath; its removal from a polyp stalk can be accomplished simply by applying gentle traction to one of the segments of the wire which protrude from the proximal end. We do not have experience in the use of the noose-type snare which can be rotated as desired. It is possible that this type may be capable of being removed from the pedicle of a polyp if the need should arise.

The reported case indicates still another recurring problem—that of retrieving all specimens of tissue which has been resected. This becomes especially important when multiple large polyps are excised. The ability to extricate a maximum of only two such lesions at a time (if a double-channel instrument is used), requiring removal and reintroduction of the colonoscope, if more lesions are to be excised, is not only uncomfortable but is also dangerous to the patient. Furthermore, loss of a specimen which may contain an invasive malignancy, may deprive the patient of the opportunity to obtain more definitive treatment and thus may eventuate in a fatal outcome.

CONCLUSION

We have described an unfortunate experience occurring during colonoscopic polypectomy with a noose-type electrosurgical snare. The need for developing instruments possessing fail-safe features is emphasized as is also the need to develop a technic which will permit retrieval of all tissue which is resected, especially when multiple specimens are involved.

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Clinical Vignette

An Unusual Case of Portasystemic Encephalopathy Caused by Splenic Vein Occlusion Following Gastrectomy

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A patient with recurrent episodes of consciousness disturbance following partial gastrectomy is presented. Angiographic examination revealed a great portasystemic shunt, which probably developed following the postoperative splenic vein thrombosis. This is suspected a rare cause of the condition.

In chronic liver disease, recurrent encephalopathy which is caused by portasystemic shunt is well known as one of the most frequent complications. It is very uncommon in adults, however, when the liver is not concerned in the shunt formation. In the present paper the authors report an unusual case of recurrent consciousness confusion which is due to the great portasystemic shunt probably caused by postgastrectomy splenic vein thrombosis.

CASE REPORT

A 54-year old man was first admitted to the hospital in May, 1976, because of poor appetite of eight months' duration. He had had partial gastrectomy for gastric ulcer at age 51 and had been treated by his home doctor for liver disease about two years prior to admission.

On the first admission, he was alert and cooperative. The liver and the spleen were not palpable and ascites was not detected. Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were moderately elevated. Indocyanine green (ICG) retention was 31% at 15 minutes. Histological findings of the percutaneous liver biopsy specimen showed chronic persistent hepatitis with inflammatory cell infiltration in the portal triad and many spotty necroses in the parenchyma. Fibrosis in the portal area was not detectable.

In June, 1976, the first episode of consciousness disturbance appeared. He was observed to be confused and disoriented but next afternoon, he became conscious and responded normally to questions and commands. Ten days after this episode, flapping tremor appeared. The deep tendon reflexes were hyperactive. Pathological reflexes of the extremities and pseudoclonus were noted. Next morning, disorientation appeared. Blood ammonia level was elevated to 353 mcg./100 ml. and an electroencephalogram revealed a triphasic wave. The neuropsychiatric symptoms spontaneously disappeared after three days.

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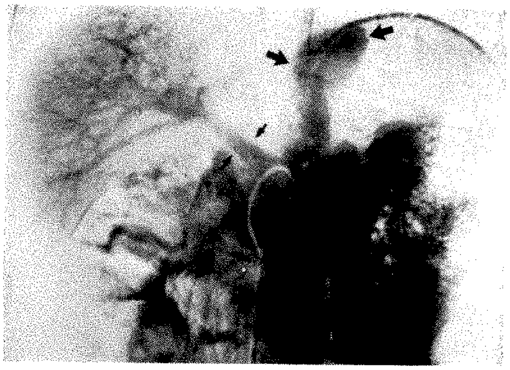

Fig. 1—Venous phase of the superior mesenteric arteriogram: a large abnormal vessel (large arrows), being emptied by the superior mesenteric vein, is revealed diverging from the portal vein (small arrows).

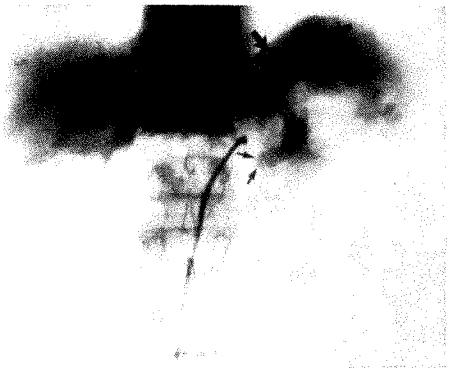

Fig. 2—Venous phase of a celiac injection: appearance of the same abnormal vessel (large arrows) as shown in Figure 1. The splenic vein obstruction (small arrows) at about 5 cm. proximal to the splenic hilus and no visualization of the portal vein.

About two months following the first biopsy, a repeat liver biopsy was done under peritoneoscopic observation. The surface of the liver was grossly even and regenerating nodules were not visualized. Parenchymal cell destruction was not as significant as in July, 1976 and he was discharged.

About six months later, he was rehospitalized because of another episode of consciousness disturbance. On examination, he was stuporous and his face was edematous. No physical signs of chronic liver disease were seen. Tendon reflexes of the extremities were exaggerated but no pathological reflexes were noted. Flapping tremor, patellar and ankle clonus were elicited.

Laboratory studies on the second admission revealed red cell count, 4.36 million; hemoglobin, 13.6 gm./100 ml.; white blood cell count, 5,500; platelets, 108,000. Erythrocyte sedimentation rate was 13 mm./hour. Fibrinogen was 190 mg./100 ml. Serum protein was 7.3 gm./100 ml. Serum alkaline phosphatase (ALP), 59 I.U.; SGOT, 41 I.U.; SGPT, 31 I.U.; lactic dehydrogenase, 129 I.U.; glutamyl transpeptidase, 14 I.U./and choline esterase was 3.0 I.U./ml. ICG retention was 36.0% at 15 minutes and blood ammonia was 233 mcg./100 ml. Hepatitis B surface antigen was negative and the antibody was positive. The serum electrolytes were normal and renal function test was within normal limits. The electrocardiogram was not remarkable. The radiograph of the chest showed no abnormal shadow. Examination of the gastrointestinal tract by an oral procedure confirmed the previous gastrectomy (Billroth I). Esophageal varices were not seen on endoscopy.

Soon after admission, colonic lavage with worm water was repeated four times every half hour. Blood ammonia levels were gradually normalized and next day, consciousness returned to normal.

For about two weeks after this episode he had been well. On the morning of 4 February he seemed to be drowsy again and fell into unconsciousness. Colonic lavage and lactulose enema were repeated for a few days with administration of L-dopa and arginine glutamate. With this regimen he recovered three days later.

Electroencephalogram, taken in three out of five episodes, showed a typical tri-

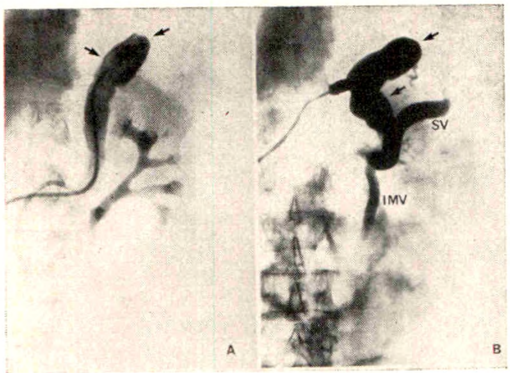

Fig. 3–Demonstration of the abnormal vessel (arrows):
A. Injection of contrast media through the catheter inserted into the inferior vena cava via the left renal vein.
B. Operative angiogram showing contrast media flowing back to the splenic vein (SV) and the inferior mesenteric vein (IMV).

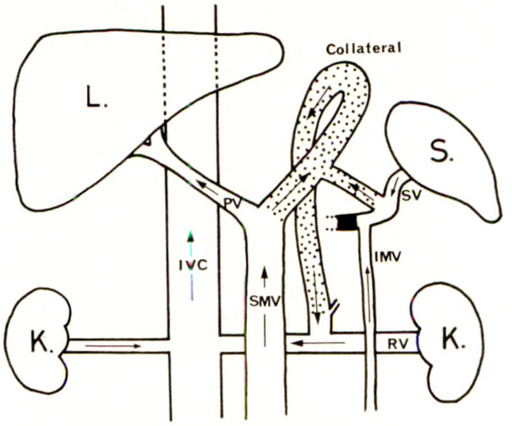

Fig. 4–Schematic representation of the portasystemic shunting. SV: splenic vein, RV: renal vein, PV: portal vein, SMV: superior mesenteric vein, IMV: inferior mesenteric vein, IVC: inferior vena cava, L: liver, S: spleen, K:kidney. Arrows show the direction of the blood flow.

phasic wave which was slightly abnormal with slow activity mingling even in the recovered period. Blood ammonia levels seemed to fluctuate grossly parallel with the clinical features. Other laboratory data seemed to have no relation to the episode of consciousness disturbance.

Histological findings of the liver were not severe enough to produce a portasystemic shunt. An angiographic examination was done to examine the possibility of extrahepatic shunt formation. The contrast medium, injected via the superior mesenteric vein, delineated the abnormal vessel which communicated with the splenic and the left renal vein (Figs. 1, 2 and 3). From these angiographic findings, it was suggested that the blood stream from both the superior mesenteric and the splenic vein flowed into the systemic circulation via the left renal vein and caused encephalopathy.

On 11 March 1977 laparotomy disclosed the obstruction of the splenic vein (Fig. 3) and shunt closure, combined with splenectomy was done.

Angiography, 17 days after shunt closure, confirmed the disappearance of the large abnormal vessel. The portal vein was dilated about 1.5 times in diameter compared to preoperation and the liver was enlarged. Laboratory data were improved; SGOT, SGPT and ALP were only slightly abnormal. Blood ammonia level was normalized and the electroencephalogram was entirely normal.

Based on these findings we assumed that portasystemic collateral was formed among the superior and inferior mesenteric vein, the splenic vein and the left renal vein (Fig. 4).

COMMENT

In chronic liver disease, especially liver cirrhosis, it has been well known that recurrent encephalopathy may occur because of portasystemic shunting.[1] The liver injury in our case was not so advanced, however, as to develop a portasystemic shunting.

The reports of recurrent encephalopathy, caused by extrahepatic portal obstruction in the absence of appreciable liver disease, is extremely rare in adults.

Extrahepatic obstruction of the portal venous system is most often the result of venous thrombosis,[2] which was predisposed by the abdominal trauma, peritonitis, obstructive carcinomatous lymph nodes, chronic pancreatitis, pylephlebitis, neonatal umbilical sepsis[3] and postoperative changes in coagulation.[4] The most usual presentation for the patients with portal venous obstruction is sudden, unexpected and often massive gastrointestinal bleeding; recurrent encephalopathy has not been described. Only one case has been reported by Chowdhury and Finestone,[5] which had recurrent episodes of encephalopathy without bleeding, following a jejunoileal by-pass operation. In their case no evidence of chronic liver disease was found and the occlusion of the portal vein and its tributaries, with consequent development of extensive collateral circulation was demonstrated by angiography. From these findings they concluded that the previous abdominal surgery was responsible for the formation of collateral resulting in encephalopathy.

In our case, there was no obvious cause to produce a splenic vein obstruction except the preceding gastrectomy. Therefore we consider that the portasystemic shunt probably occurred because of the postoperative splenic vein thrombosis.

ACKNOWLEDGMENTS

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Clinical Vignette

Squamous Cell Carcinoma of the Stomach

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Squamous cell carcinoma of the stomach is a rare, unusual lesion which tends to occur at a somewhat earlier age than adenocarcinoma. Grossly and radiologically the tumor is indistinguishable from adenocarcinoma and may involve any portion of the stomach. Although the pathogenesis of this lesion remains unclear, most authors favor the "metaplastic theory" for the development of the tumor. In this case it is felt that the tumor probably arose from gastric squamous mucosa present congenitally in the lesser curvature.

Pure squamous cell carcinoma of the stomach is extremely rare even though gastric carcinoma remains one of the commonest adult gastrointestinal malignancies. Only 39 cases of this entity have been reported in the world literature.[1-4] The pathogenesis of this unusual tumor remains uncertain.

CASE REPORT

The patient was a 55-year old well developed Trinidad-born black woman who was admitted to Kings County Hospital with a history of postprandial mid epigastric pain and vomiting. Her pain had been alleviated somewhat by anticholinergics. Over the course of the preceding year the patient had shown a significant weight loss of 4.5 kg. On physical examination she appeared slightly emaciated, her abdomen was flat and soft with mid epigastric tenderness to deep palpation. No mass was palpable. Hepatomegaly was not noted. The laboratory studies showed a hematocrit of 34.1%; hemoglobin, 11.8 mg.%; WBC, 7,700/cu. mm. with a normal differential; the remainder of the laboratory tests were unremarkable. An upper gastrointestinal series demonstrated an extensive tumor involving the lesser curvature of the stomach from just below the fundus to the antrum. There was both nodularity and rigidity of the involved portion of the stomach. Barium was seen to penetrate crevices within the tumor mass (Fig. 1). At gastroscopy several superficial ulcers were visualized at the gastroesophageal junction. When the gastroscope was passed into the cardia some resistance was felt and a large, fungating, friable and ulcerated lesion, which involved the entire lesser curve of the stomach up to the distal antrum was encountered. The duodenum was normal.

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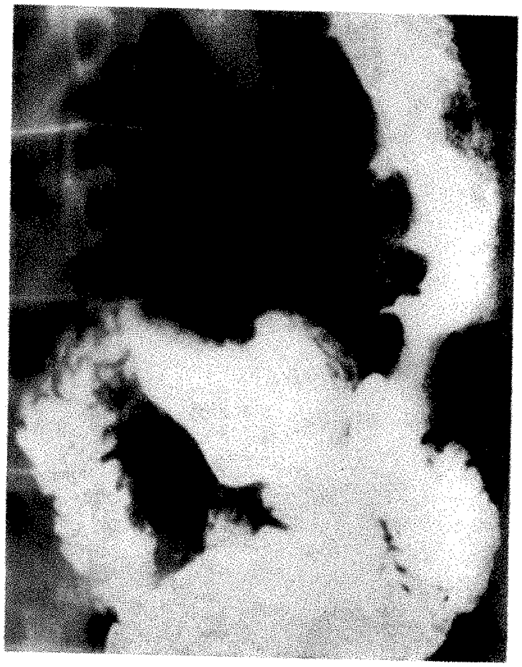

Fig. 1—Barium meal: Extension tumor nodularity and ulceration are evident along the lesser curvature of the stomach.

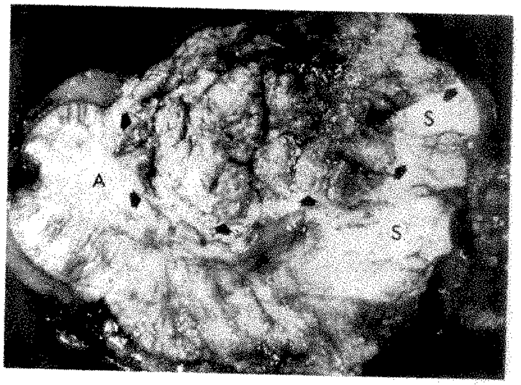

Fig. 2—Gross appearance of the resected specimen (specimen open along the greater curvature). Note the large, fungating, ulcerated tumor mass (arrows) present on the lesser curvature and extending to the antrum (A). The gastric mucosa proximal to the tumor (and distal to the esophagus) is white and shiny (S).

Multiple biopsies taken from the lesion and gastric washings were sent for cytology. The biopsy indicated the presence of an invasive well differentiated squamous cell carcinoma devoid of any glandular differentiation. Malignant squamous cells were also identified in the gastric washings.

At laparotomy the presence of an extensive tumor of the gastric lesser curvature was corroborated. Frozen sections confirmed that the tumor was a squamous cell carcinoma. The liver appeared free of metastatic tumor. A total gastrectomy together with a partial pancreatectomy and splenectomy were performed.

PATHOLOGY

The main specimen (Fig. 2) consisted of a stomach with attached distal esophagus and pyloric stump. A large nodular and ulcerated tumor mass measuring 10 × 6.2 cm. occupied the entire lesser curvature and extended to the pyloric antrum. The central portion of the neoplasm was ulcerated and showed a necrotic base. On section the tumor was soft, pink-gray in color and with well defined borders. The entire thickeness of the gastric wall was involved by the tumor which had infiltrated into the perigastric fat. The remainder of the gastric mucosa appeared grossly normal except the region between the esophageal margin and the neoplasm on the lesser curvature which was smooth and had a shiny, white appearance resembling normal esophageal mucosa.

Microscopically this area was found to be squamous mucosa devoid of any dysplastic or *in situ* malignant changes. Careful examination showed only a few glands beneath the squamous epithelium. These glands were not clearly identifiable as mucous in character (as in the normal lower esophagus) nor gastric in type (neither parietal nor zymogenic chief cells were identified). There was an abrupt change between squamous mucosa lining the proximal stomach and the adjacent neoplasm (Fig. 3).

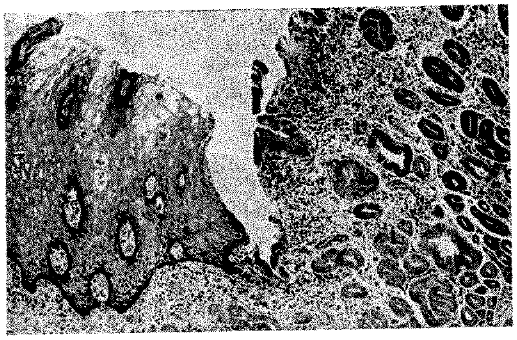

Fig. 3—Area showing the abrupt change from the gastric squamous epithelium (left) to the normal gastric mucosa (right). Marked inflammation is present in the mucosa (Hematoxylin and eosin, original magnification x63).

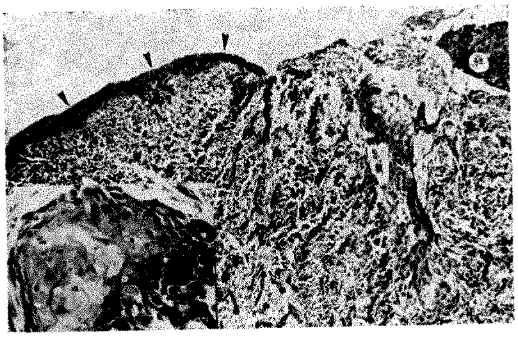

Fig. 4—Gastric squamous mucosa (arrowheads) and adjacent invasive squamous cell carcinoma (right) in an area with marked inflammatory background (Hematoxylin and eosin, original magnification x25). Inset: High power view of cluster of invasive tumor cells showing early keratin pearl formation (Hematoxylin and eosin, original magnification x250).

The tumor was a well differentiated squamous cell carcinoma with frequent keratin pearl formation. Intercellular bridges and keratinization were often prominent features (Fig. 4). Some areas of the neoplasm showed clusters of cells which were less well differentiated and exhibited marked pleomorphism and frequent mitoses. The intervening stroma was edematous and myxoid in appearance. There was no evidence of glandular differentiation in the tumor, thus eliminating the possibility that the neoplasm was an adenosquamous carcinoma (the tumor was also examined for this purpose by electron microscopy). Severe chronic inflammatory changes were noted throughout the stomach together with areas of focal mucosal atrophy. The esophageal and pyloric resection margins were free of tumor involvement. Thirty lymph nodes were examined and showed no evidence of metastasis.

COMMENT

The lesion described was unquestionably a pure squamous cell carcinoma. There has been no evidence of a similar tumor elsewhere in the patient including the esophagus in five months of follow-up, consequently eliminating the unlikely possibility that the tumor could have been metastatic to, and not primary from, the stomach. The tumor arose in an area lined by squamous mucosa which was continuous with that of the esophagus but located well within the stomach. For all the aforementioned reasons the tumor fulfills the criteria of pure squamous cell carcinoma of the stomach.

The pathogenesis of this neoplasm remains obscure and controversial. Several possible mechanisms have been postulated to explain its occurrence and location. The neoplasm could arise from pre-existing gastric squamous mucosa present congenitally either as isolated foci or in continuity with that of the esophagus. These congenital anomalies are rare. In addition, the presence of gastric squamous mucosa can represent an acquired phenomenon which may be due to down-growth of esophageal mucosa as may ensue in cases of chemical esophagogastric injury.[4] It may also be due to local squamous metaplasia as Boswell and Helwig[1] and others[6-9] have demonstrated in the vicinity or margins of gastric peptic ulcers and in gastric tuberculosis. Furthermore, Fütterer[10] has produced experimental evidence that gastric squamous metaplasia can be induced by artificially delaying the healing of gastric mucosal lesions. Other authors[11-14] have tried to induce the development of squamous metaplasia in the stomach of laboratory animals by means of dietary changes. They, however, were only able to demonstrate ulcerative and subsequent proliferative mucosal changes of nonmetaplastic nature.

Wood[15] suggested that gastric squamous cell carcinoma could arise directly from stimulated undifferentiated basal epithelial cells without an intervening stage of squamous metaplasia. In support of his theory he cited experimental work by Stewart and Lorenz[16, 17] who demonstrated the occurrence of a variety of neoplasms, including squamous cell carcinoma and adenoacanthoma subsequent to the injection of methylcholanthrene into the gastric wall of mice without evidence of metaplastic change.

A recent theory to explain the development of gastric squamous cell carcinoma has been suggested by Straus, et al.[3] These authors state that since they know of one case of tibial adamantinoma[18] which appears to have had demonstrable origin in vascular endothelium, and the latter is a variety of simple squamous epithelium,[19, 20] the endothelium of gastric vessels could give rise to squamous cell carcinoma. Among other objections to this theory is the fact that there is no known instance of a metaplastic or hyperplastic vascular endothelium showing keratinization, as all gastric squamous carcinomas do.

It is most likely this neoplasm arose from the pre-existing gastric squamous mucosa. A stage of local dysplasia, subsequently overrun by the neoplasm probably preceded the development of the invasive tumor. This gastric squamous mucosa was likely present on a congenital basis and not an acquired development following local injury, as has been recorded with acid or lye burns. In the latter instance a degree of scarring beneath the squamous lining and an associated history would have been expected. Unfortunately, it was not possible to ascertain whether the glands found beneath the gastric squamous were of gastric or esophageal origin.

Our review of the literature shows that squamous cell carcinoma of the stomach occurs in a somewhat younger age group than adenocarcinoma[1] and that male preponderance is far greater in the ratio 5:1.[1]

The radiological appearances of the lesion are protean. The tumor may present in any segment of the stomach from the fundus to the antrum with the pylorus the most commonly involved area. Nodular, ulcerating, scirrhous and stenosing lesions have all been described.[1-3, 21] There is no clear cut way of differentiating squamous cell carcinoma from adenocarcinoma of the stomach on the basis of radiological findings alone. Some reported cases of gastric squamous cell carcinoma have displayed a lesser tendency to local spread as well• as metastasis[2] and Parks[21] reported a patient with a seven year postoperative survival. Boswell and Helwig's series, however, shows that all of their 12 patients died within seven months of surgery from local and distant metastases.

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Clinical Vignette

Occlusion of the Hepatic Veins by an Adrenal Carcinoma

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Occlusion of the main hepatic veins (Budd-Chiari syndrome) is most commonly due to thrombosis associated with disorders of blood coagulation. We report the details of a patient with the Budd-Chiari syndrome caused by obstruction of the hepatic veins by an adrenocortical carcinoma.

CASE REPORT

A 30-year old housewife presented with a four-week history of progressive dyspnea, left hypochondrial pain and abdominal distention. She had developed secondary amenorrhea 12 months previously but had never taken the contraceptive pill.

She was thin, dyspneic at rest and cyanosed. There was diminished air entry at the base of both lungs. There was gross ascites and a tender liver was palpable below the costal margin, with a separate mass below the left costal margin. She was slightly hirsute with acne and atrophic breasts but normal external genitalia.

Initial investigations revealed: serum alkaline phosphatase, 35 K.A. U./100 ml. (normal range 3-13); aspartate aminotransferase, 125 I.U./l. (0-50); normal serum bilirubin and albumin levels and prothrombin time ratio. Chest x-ray showed normal lung fields with elevated diaphragms. There was severe arterial hypoxemia with hypocapnia. A ventilation-perfusion lung snap showed evidence of bilateral pulmonary emboli and she was therefore anticoagulated. A liver snap showed patchy, uptake of colloid by an enlarged liver but no splenomegaly. Intravenous urography showed a normal right kidney but there was a mass containing flecks of calcification compressing the left renal substance and distorting the pelvicalyceal system. Ureterograms confirmed the compressed calyces and a renal arteriogram showed a large vascular mass displacing the aorta and the splenic and left renal arteries. Urinary excretion of steroids were: 17-oxosteroids, 491 μmol/day (normal range 17-52 μmol); 17-oxogenic steroids, 322 μmol/day (14-55 μmol); dehydroepiandrosterone, 52 μmol/day (< 5 μmol) and free cortisol, 232 nmol/day (44-220 nmol). Urinary vanylmandelic acid excretion was normal.

At laparotomy ascites was confirmed and a very large vascular tumor was found in the region of the upper pole of the left kidney. The liver was grossly enlarged and engorged with blood. The left renal vein was distended and occluded by tumor which extended up the inferior vena cava

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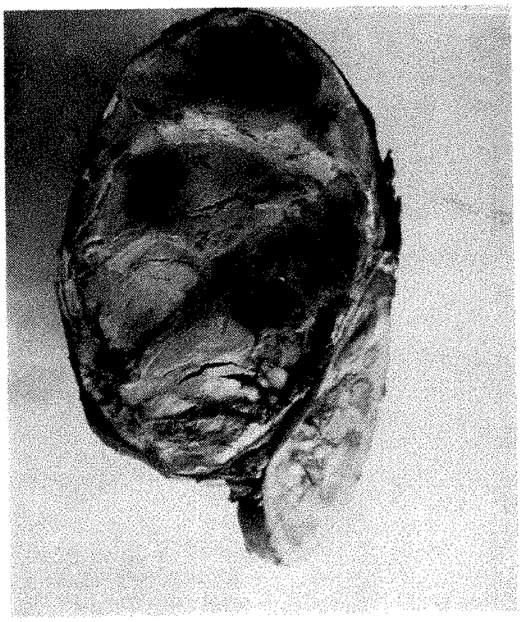

Fig. 1—Operative specimen illustrating the left kidney and adrenal tumor.

beyond the hepatic vein ostia. The left kidney and suprarenal mass were removed. Postoperatively large quantities of ascites drained from the abdominal wound and the patient died on the fifth postoperative day.

Examination of the operative specimen (Fig. 1) showed a primary adrenocortical carcinoma, 12 × 13 × 18 cm. and weighing 2.3 kg., which was compressing but not invading, the renal substance. There was, however, extensive invasion of the renal and adrenal veins. Postmortem examination revealed complete occlusion of the inferior vena cava by thrombus and tumor, occlusion of the hepatic veins with antemortem thrombus and intense hepatic venous congestion. There were multiple pulmonary emboli containing tumor and thrombus. The right adrenal gland was of normal size and showed lipid depletion in the *zona fasciculata.*

COMMENT

Various malignant tumors have been reported to occlude the hepatic veins,[1, 2] including renal adenocarcinomata, primary and secondary hepatic carcinomata and leiomyosarcomas[3] but occlusion by primary adrenocortical carcinoma is rare[4-6] and has not previously been diagosed before death. Copinschi, et al,[7] however, reported a patient in whom, several months after removal of a primary adrenal carcinoma, occlusion occurred when the tumor extended up the inferior vena cava. This tumor also caused virilization. In our patient the absence of the clinical features of Cushing's syndrome and the normal right adrenal gland suggest that the tumor was secreting inactive precursors of cortisone in addition to androgens.

We suggest that the rare development of the Budd-Chiari syndrome in a patient with a cushingoid appearance or virilization should raise the possibility of an underlying adrenal tumor.

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Clinical Vignette

Universal Colitis

DIAGNOSTIC SIGNIFICANCE OF MUCOCUTANEOUS LESIONS

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INTRODUCTION

When nonspecific colitis involves the whole colon without skip areas or ileal disease, the most likely diagnosis is ulcerative colitis. Crohn's disease may occasionally present as acute universal colitis[1] but confirmation of the diagnosis may be difficult except in instances where classical histological changes are noted at biopsy. The occurrence of mucocutaneous lesions may, however, tilt the balance in favor of either entity even though some lesions may be common to both.[2, 3] In doubtful situations, biopsies may aid diagnosis, as exemplified by the case described.

CASE REPORT

A 34-year old black male presented with a six-day history of malaise, fever and watery diarrhea, 10-15 times, containing mucus but no blood. He had some lower abdominal pain aggravated by bowel movements. There was no history of recent conjunctivitis, myalgias, arthralgias, skin rash or travel outside the United States.

Two years previously the patient had been admitted to this hospital because of hematochezia for a few days. Sigmoidoscopy had shown nonbleeding external and internal hemorrhoids. The mucosal surface appeared indurated with scattered ulcerations. Biopsy showed mononuclear cellular infiltration of the mucosa and submucosa and chronic ulcerations with areas of granulation tissue. Barium enema revealed mild serration and ulceration of the mucosa limited to the rectosigmoid area. The patient was discharged with a presumptive diagnosis of nonspecific proctocolitis and treated with azulfidine.

His symptoms subsided and he was subsequently lost to follow-up. Until the present admission, however, he claimed he had been totally asymptomatic and had discontinued azulfidine for the past one and a half years.

Physical examination showed a well nourished, nonicteric male with moderate abdominal discomfort. Temperature was 38.5° C; pulse, 84/min. and blood pressure, 120/77 mm. Hg. The abdomen was scaphoid with no masses, organomegaly or tenderness. Bowel sounds were normal. Extremities showed no clubbing, joint abnormalities or skin lesions. Rectal examination demonstrated no abnormality but the yellowish liquid stool was positive for blood.

Laboratory data showed a hemoglobin of 14.3 gm.%; hematocrit, 43%; white cell count of 9,500/cu. mm. with 48% polymorphonuclear leucocytes, 16% bands,

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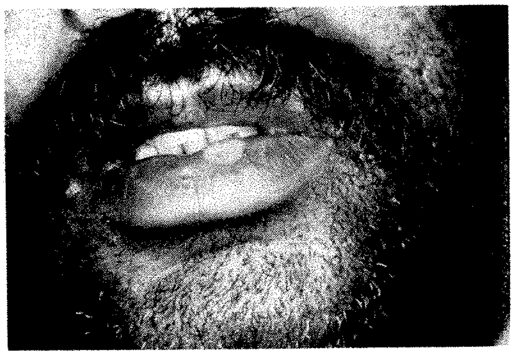

Fig. 1—Labial ulcer during early healing phase.

34% lymphocytes and 2% eosinophils. The bilirubin was 0.4 mg./100 ml.; SGOT, 21 I.U./ml.; LDH, 316 I.U./ml.; total protein 7 gm./100 ml. with albumin 4.1 gm./100 ml. Flat plate of the abdomen showed nonspecific small intestinal gas pattern. Direct smear of the stool showed some gram negative rods, occasional red blood cells, some polymorphonuclear leucocytes and epithelial cells. No ova or parasites were seen. Repeated fresh stool specimens did not show any ameba. Stool culture for shigella and salmonella was repeatedly negative.

Sigmoidoscopy, performed on the second day after admission, showed the rectal mucosa to be erythematous and indurated with scattered deep ulcerations extending up to 20 cm. from the anal verge. Biopsies were taken and histologic examination showed diffuse lymphocytic infiltration of the mucosa and submucosa, prominent lymphoid follicles, lymphangiectasia, mucosal ulceration and presence of a fissure extending into the submucosa.

On the fourth hospital day parenteral fluids and hydrocortisone therapy were started. The fever subsided but the watery diarrhea continued unabated. On the sixth hospital day a few small skin ulcerations, each about 5 mm. in diameter, were noted on the extremities. Examination of the mouth showed a punched-out ulcer with raised nodular margins, 1 cm. in diameter, on the left tonsil and a similar ulcer, 7-8 mm. in diameter, on the mucus membrane of the lower lip (Fig. 1). Biopsy of the labial ulcer showed extensive mononuclear cell infiltration of the submucosa, lymphoid hyperplasia, lymphangiectasia, neuronal hyperplasia and an early epitheloid granuloma. Fungal stains were negative. A perianal sinus opening and a big scrotal ulcer, 3-4 cm. in diameter, with an irregular base and deeply undermined margins, were noted for the first time (Fig. 2). Biopsy of the scrotal ulcer showed chronic inflammatory cell infiltration of the dermal layers with granulation tissue formation, compatible with *pyoderma gangrenosum.*

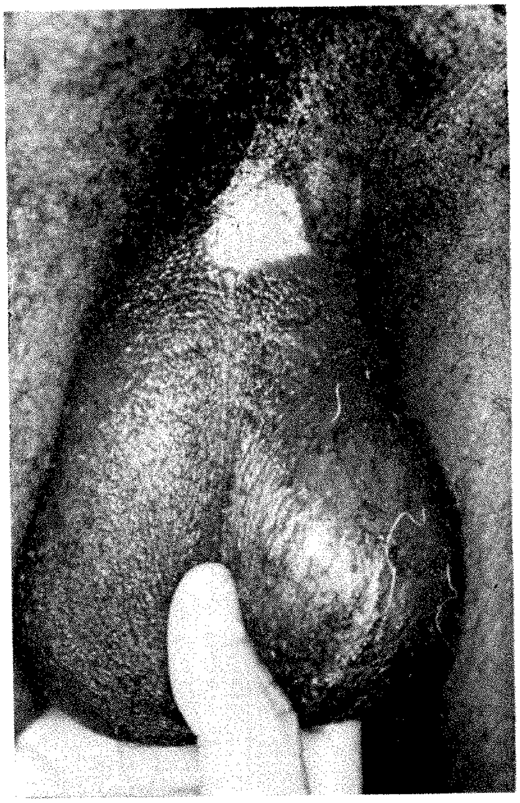

Fig. 2—Scrotal ulcer in healing phase.

A barium enema showed disease extending from the rectum to the cecum. The

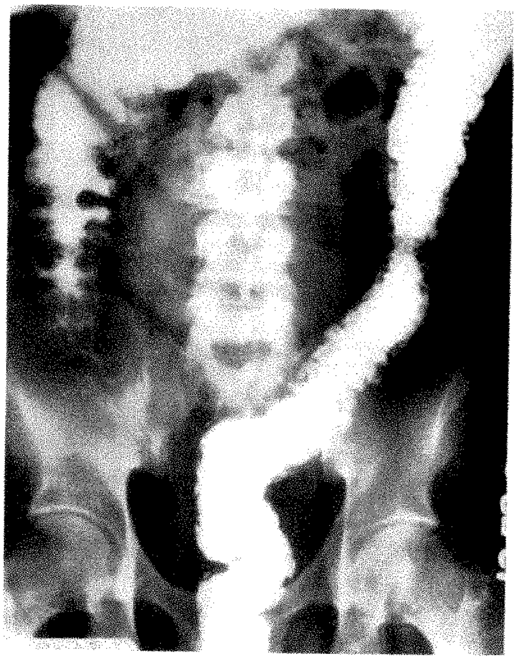

Fig. 3—Barium enema examination. Note the involvement of the entire colon and the presence of longitudinal submucosal sinus tracts.

mucosa appeared shaggy with multiple deep ulcerations and a few longitudinal submucosal communicating tracts (Fig. 3). An upper gastrointestinal and small bowel series showed a normal terminal ileum. A dye study of the perianal sinus showed a 6 cm. long, fistulous tract with no internal communication.

The patient began to show increasing clinical response by the third hospital week. The diarrhea subsided to two to three formed bowel movements daily. The skin and oral ulcerations healed completely and the scrotal ulceration was reduced to half its original size. He was continued on oral prednisone 40 mg. daily and started on azulfidine which was gradually increased to 6 gm. daily.

A sigmoidoscopy repeated on the 28th hospital day showed marked improvement. Scattered small ulcerations were still seen but the intervening mucosa appeared normal.

The patient was discharged at the end of the 5th hospital week on prednisone 20 mg. and azulfidine 6 gm. daily.

COMMENT

Our patient presented with symptoms of acute colitis. Even after sigmoidoscopic and barium enema examinations and evaluation of rectal biopsies, a definite differentiation between ulcerative colitis and Crohn's colitis could not be made. The subsequent development of mucocutaneous lesions with pathognomonic histologic findings, however, gave us an indication of the true nature of the disease.

Oral mucosal lesions have been reported in both types of colitis.[2-10] In ulcerative colitis the common oral lesion is an aphthous stomatitis or ulcer.[2] The latter is noted to be irregular in shape with rolled margins and covered by a greyish white slough. In Crohn's disease two main types of oral lesions have been described, namely, aphthous stomatitis and actual granulomatous disease of the mouth.[3] The latter more characteristic lesions have been described as relatively deep, linear ulcers with somewhat nodular hyperplastic margins and clean base. Occasionally, there are areas of marked mucosal hyperplasia with deep surface fissuring giving it a cobblestoned appearance. Microscopically, the finding of an epithelioid granuloma, as in our patient, may be considered diagnostic of oral Crohn's disease.[11] Nevertheless, previous limited experience of similar lesions has shown that a granuloma may be found only in less than 10% of biopsies.[3] Other evidence supporting oral Crohn's disease may be present in the form of abnormal focal collections of lymphocytes and perivascular infiltrates of mononuclear cells in the *lamina propria* and submucosa and stromal connective tissue.[12] Neural hyperplasia, lymphangiectasia and edema, also noted in our patient's biopsy, may be indicative of nonspecific chronic inflammation.[12] The changes described in oral mucosal biopsies of ulcerative colitis patients are quite distinct with polymorphonculear and eosinophilic infiltration of the *lamina propria* and perivascular deposition of fibrin.[3]

The scrotal ulcer also had sharp margins similar to the oral lesions. Biopsy was consistent, however, with *pyoderma gangrenosum*. This lesion has been rarely noted to occur in patients with Crohn's colitis[2, 13] and its presence could possibly have misled us to a diagnosis of ulcerative colitis.

This patient exemplifies the rare situation when different types of mucocutaneous lesions occurred in association with Crohn's colitis. Macroscopic appearances were misleading. Biopsies clarified the actual nature of the lesions and even helped categorize the type of colitis.

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Clinical Vignette

Bronchial Asthma Associated with Intestinal Parasites

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Fifty patients with bronchial asthma and 50 normal controls were studied in Hacettepe University Medical Center. Forty per cent of the patients with bronchial asthma and 14% of the controls had ascarides in the stool examinations. The significant difference in these two groups indicates that intestinal parasites, should be looked for in the patients with bronchial asthma.

Ascariasis is a wide spread helminthic infection which is seen in about one-fourth of the world population. Although clinical findings may generally be overlooked or considered unimportant, they may sometimes lead to serious complications such as intestinal and bile duct obstruction and pulmonary abcesses.

The larvae which migrate from the intestine to the lungs may cause respiratory system symptoms such as asthma and Löffler's syndrome. Allergic symptoms such as urticaria, hay fever and asthma are more frequent in children with ascariasis.[1,2] It has been observed that when the skin test is performed with the antigens, (prepared from ascarides) they may cause bronchial asthma-like attacks in some patients. A typical clinical picture of bronchial asthma is also observed in people who eat the food infected with the ascaris suum eggs.[3]

These observations led us to investigate the incidence of intestinal parasites in patients with bronchial asthma.

MATERIAL AND METHODS

Fifty patients with bronchial asthma and 50 normal controls were studied at Hacettepe University Medical Center. The ages of the patients ranged from 14-61. The patients had symptoms of bronchial asthma for four to 21 years. The subjects of the control group ranged in ages from 14-19. The difference in age ranges between the two groups was a result of the control group being taken from students at the Hacettepe Nursing College. They were selected because they were children of families whose socioeconomic standards were generally average or low. It was easier for us to use them as a control group and we expected a higher incidence of parasites in the group. We know that there exists a close relationship between the environmental health conditions and the presence of parasites. The majority of patients with bronchial asthma had a good living standard and came from a better section. Thus the difference would be more significant.

Stool specimens were taken at three different times from each patient and from each control and were examined by the method described by Ritchie.[4]

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RESULTS

Ascaris was found in 20 out of 50 patients with bronchial asthma (40%). In the remaining 30 patients, seven had taenia and one patient had *ancylostoma duodenale*. In the control group only seven out of 50 cases had ascaris (14%). Two cases had taenia and one had *ancylostoma duodenale*.

COMMENT

The relation between bronchial asthma and intestinal parasites has been known since 1962. David and Tullis[5] studied 201 patients with bronchial asthma and they found that 93% had *Ascaris lumbricoides*, 6% had *Strongyloides stercoralis* and 1% had *Necator americanus*. Van Dellen and Thompson[6] found ascariasis in 60 out of 123 patients with bronchial asthma (49%). In these studies the incidence of intestinal parasites is higher in comparison to our study. Fungal spores and pollens are frequently encountered in the stool examination of the patients suffering from bronchial asthma. Morphologically they resemble *Ascaris lumbricoides* eggs. If they are not studied carefully, it is difficult to differentiate them. For this reason, an error must be considered in all of these patients.

The incidence of intestinal parasites, especially *Ascaris lumbricoides*, is higher in the patients than the controls. This finding suggests that these parasites may be responsible for the etiology of bronchial asthma in these patients. Each patient with bronchial asthma should be checked for intestinal parasites and after the elimination of the parasites, specific therapy should be instituted.

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The Pediatric Corner

ENDOSCOPIC EVALUATION OF UPPER GASTROINTESTINAL BLEEDING IN THE NEWBORN

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A case of upper gastrointestinal bleeding in the first 24 hours of life is discussed. The application and importance of upper gastrointestinal fiberoptic endoscopy in establishing a precise diagnosis in this age group, not previously reported, is demonstrated.

Localization of upper gastrointestinal hemorrhage often represents a difficult diagnostic problem in the newborn period.[1-3] This case report describes a newborn with upper gastrointestinal hemorrhage due to gastric erosions, visualized with fiberoptic endoscopy during the first 24 hours of life, an experience not previously reported.[4, 5]

CASE REPORT

A male infant weighing 3,400 gm. at birth developed hematemesis and melena six hours after birth. Pregnancy, labor and delivery were uncomplicated. Apgar scores were 9 at one and five minutes. There was no family history of hemorrhagic diathesis.

Estimated blood loss was 60-70 cc. and the hemoglobin level decreased from 15.9 to 13.8 gm.% The baby was treated with Vitamin K_1, 1 mg. intramuscularly and with 5% dextrose in normal saline administration through an umbilical arterial catheter. Upon transfer to the University of California Medical Center, initial examination revealed pallor and mild icterus. There were no petecchiae, purpura, or ecchymoses. The remainder of the examination was unremarkable. The initial laboratory data included hemoglobin, 10.5 gm./100 ml.; hematocrit, 31.2%; prothrombin time, 14.2 sec. (control 11.0 sec.); partial thromboplastin time, 31.3 sec. (normal less than 36 sec.). Serum calcium, phosphorous, total protein, albumin, glucose, fibrinogen and total platelet determinations were within normal limits. Upper gastrointestinal series and chest x-rays were negative.

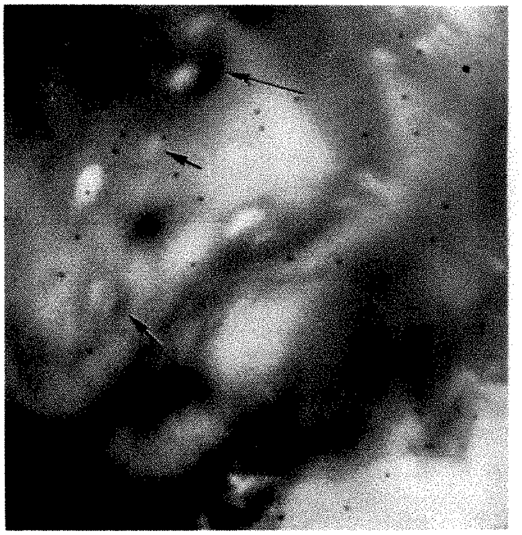

Fig. 1—Multiple superficial erosions are present along the greater curvature of the body of the stomach (short arrow). An adherent clot is marked by the long arrow.

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At less than 24 hours of age, fiberoptic esophagogastroduodenoscopy was performed under sedation with the Olympus GIF-P_1 instrument. Many superficial erosions were observed in the body of the stomach and on the greater and lesser curvatures, with two areas of adherent clots (Fig. 1).

Treatment consisted of nasogastric lavage with cold saline and subsequent suction for 24 hours. Because of religious affiliation, permission for blood or plasma administration was not obtained. The baby received 5% dextrose in normal saline through the umbilical catheter, and Vitamin K_1, 2 mg. I.M. The subsequent clinical course was uneventful. Breast feedings were instituted without difficulty, and the patient was discharged at six days of age.

COMMENT

Upper gastrointestinal hemorrhage generally occurs during the first 48 hours after birth.[6] In this period, evaluation of specific causes such as hemorrhagic disease of the newborn, stress ulcer, peptic esophagitis or gastritis and esophageal varices is frequently complicated by the presence of swallowed placental blood in the stomach.[6] One major cause, swallowed maternal blood, can be determined by the Apt-Downey test for the presence of fetal hemoglobin in gastric contents.[3, 6] With standard radiographic technics, the source or cause of this type of hemorrhage remains undetermined in more than 50% of newborns, especially when the bleeding is massive.[6, 7] The effectiveness, accuracy and safety of fiberoptic endoscopy has been established in the pediatric age group.[4, 5, 8] Its superior diagnostic ability in upper gastrointestinal hemorrhage in children, including older neonates and infants, has also been demonstrated.[4, 5, 8]

This reported case illustrates the potential usefulness of fiberoptic endoscopy, by qualified physicians, in elucidation of upper gastrointestinal bleeding in the immediate newborn period, thereby ensuring appropriate specific treatment, based on precise diagnosis.

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The Radiology Corner*

LOCALIZED GIANT PSEUDOPOLYPOSIS OF THE COLON

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Localized giant pseudopolyposis is a rare complication in patients with inflammatory diseases of the colon which produces a huge intraluminal polypoid mass. Examples are described in a child with chronic ulcerative colitis in whom the lesion filled the rectum and in an adult with recurrent granulomatous ileocolitis in whom the mass was present in the transverse colon adjacent to a stenotic anastomosis. The clinical presentation, radiologic features and pathologic findings of this unusual sequela to inflammation are reviewed.

Editors' note:—In recent years several papers have appeared describing large numbers of inflammatory polyps in ulcerative colitis, producing obstruction to the retrograde flow of barium. These polyps are usually segmental in distribution and of considerable size. Similar inflammatory polyps are now being described in Crohn's disease. These, however, are usually smaller and produce less obstruction. Although in both conditions significant retrograde obstruction may occur, antegrade obstruction is rare. The large inflammatory polyps have no relation to carcinoma.

Pseudopolyposis is commonly seen in patients with inflammatory disease of the colon. It is the most frequent local sequel of ulcerative colitis occurring in 12-19% of all patients with this disease.[1-6] Rarely this postinflammatory response is remarkably exuberant, creating a huge, localized colonic mass. We present two cases of localized giant pseudopolyposis; one in a pediatric patient with chronic ulcerative colitis and the other in an adult with chronic granulomatous ileocolitis.

CASE REPORTS

Case 1:—C. S., a 10-year old girl, was admitted because of increasing constipation. A diagnosis of ulcerative colitis had been established one year earlier and the patient was being treated with prednisone and Azulfidine®. A barium enema examination, six months prior to admission, showed multiple pseudopolyps throughout the colon. There was an episode of "rectal prolapse" treated three months prior to admission.

Initial contrast enema examination demonstrated complete obstruction to the retrograde flow of barium by a large intraluminal mass in the rectum (Fig. 1). This was interpreted as due either to feces or an intussusception. Sigmoidoscopy revealed a polypoid lesion covered with multiple filiform projections and a biopsy showed

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[*] Edited by Richard H. Marshak, M.D., F.A.C.G. and Arthur E. Lindner, M.D., F.A.C.G.

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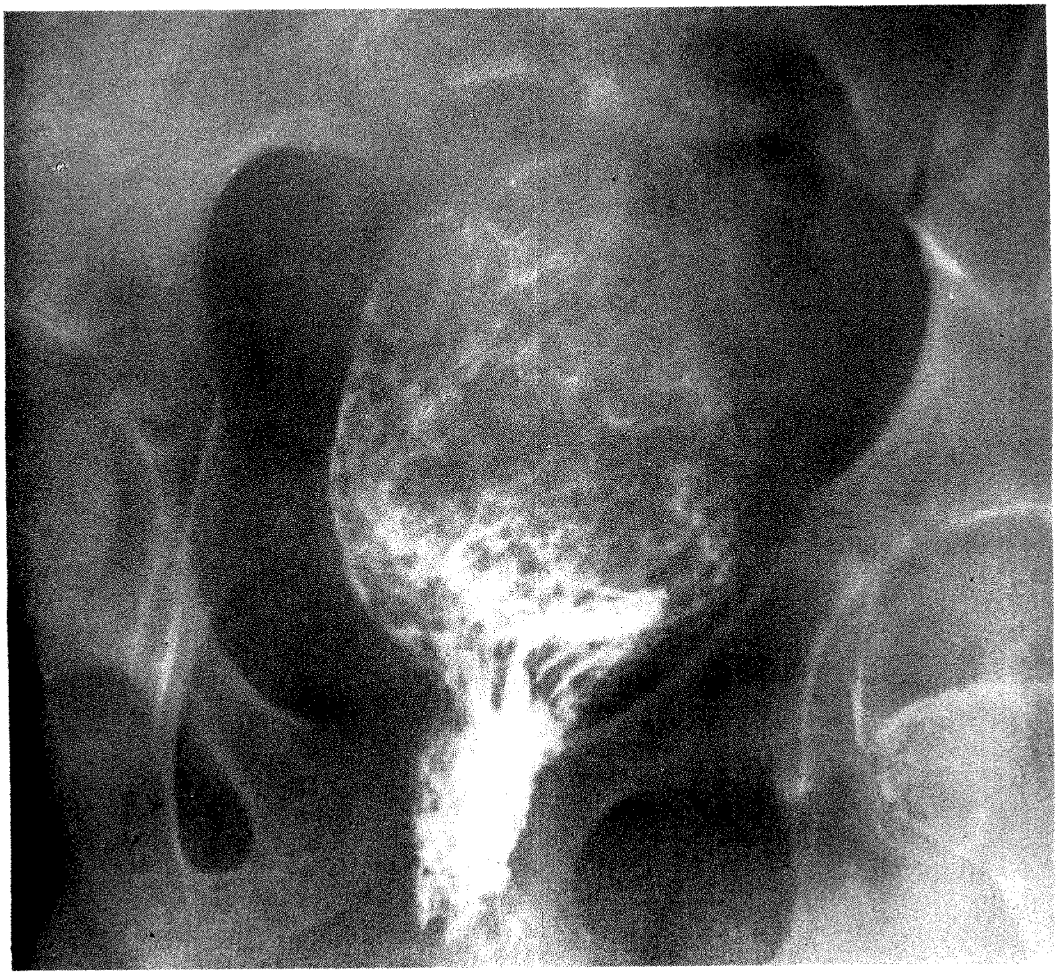

Fig. 1—Case 1, initial barium enema examination. There is complete obstruction of the rectum by a large irregular intraluminal mass.

pseudopolyposis. A catheter was passed through the mass under direct vision at sigmoidoscopy through which a second barium enema examination was performed (Figs. 2 and 3). The rectal mass was again demonstrated. In addition, multiple linear radiolucencies were evident throughout the colon.

A total colectomy and ileostomy were subsequently performed. The serosal surface of the colon was normal. Upon opening the bowel, numerous pseudopolyps were noted throughout the colon. These excresences had multiple bifurcations and the mucosa of the colon resembled a "shag carpet". There was a large polypoid mass of pseudopolyps located in the rectum. Numerous, fine filiform, mucosal strands extended from the surface of the mass across the bowel lumen from one pseudopolyp to another.

Microscopically, there was extensive mucosal proliferation forming massive pseudopolyps. The entire mucosa of the colon showed acute, subacute and chronic inflammation with abundant crypt abscess formation. There was no evidence of malignant change. Pathologic diagnosis was

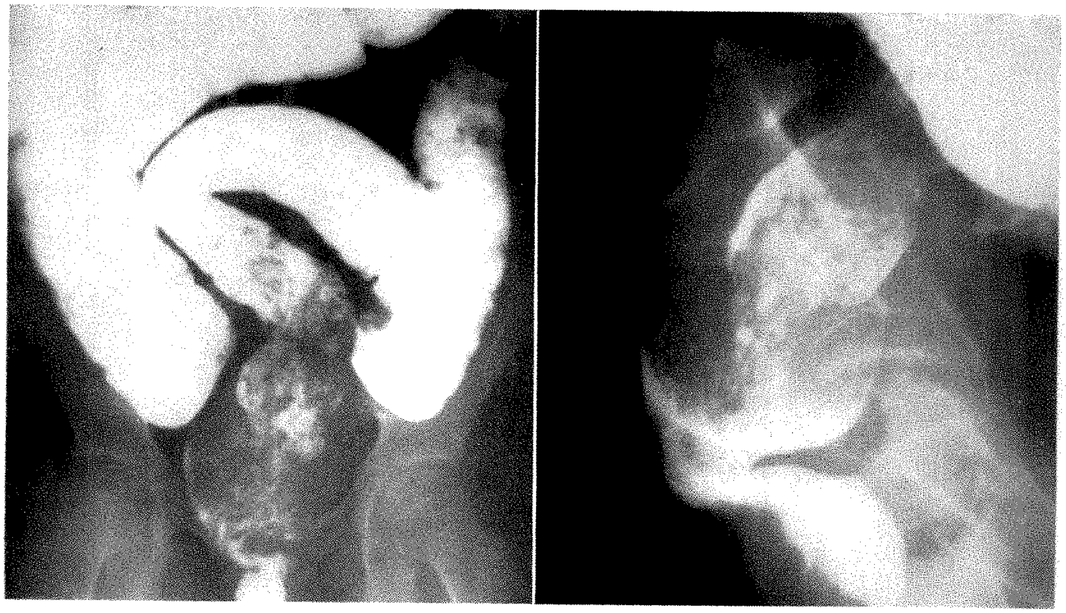

Fig. 2 Fig. 3

Figs. 2 and 3—Frontal and lateral projections of a second barium enema examination performed via a tube inserted through the mass under direct vision at sigmoidoscopy. There is a large shaggy mass in the rectum. Multiple pseudopolyps are present in the ascending and descending colon.

chronic ulcerative colitis with florid universal pseudopolyposis and localized giant pseudopolyposis in the rectum.

Case 2:—R. J. was a 57-year old white man with a long history of Crohn's disease. At age 29, the diagnosis of Crohn's disease involving the last 25 cm. of the terminal ileum was established when a laparotomy was performed with the mistaken preoperative diagnosis of acute appendicitis. Four years later, the patient underwent a resection of the terminal ileum, cecum and ascending colon with a right transverse ileocolostomy. The patient did well clinically until six months before the present admission when abdominal pain and diarrhea recurred. A barium enema examination, performed at that time, showed recurrence of Crohn's disease in the last 25 cm. of the ileum and in the right half of the transverse colon. Despite treatment with Azulfidine and prednisone, crampy abdominal pain persisted and the patient was admitted to the hospital. Another barium enema examination confirmed the presence of granulomatous ileocolitis but also demonstrated an exuberant, nodular mass filling the lumen of the right transverse colon adjacent to the anastomosis (Fig. 4). The remainder of the colon was normal except for mild spastic colon disease involving the sigmoid. The distal 25 cm. of the ileum were abnormal with spasm and edema of the mucosa. Because the anastomosis was narrow (Fig. 5), the diagnosis of partial obstruction was made and the patient underwent a second ileocolic resection with an anastomosis in the descending colon.

Pathological examination of the resected specimen showed granulomatous ileocolitis with narrowing of the anastomosis. The right portion of the transverse colon was filled with irregular nodular excrescences which completely encircled the mucosal surface. Microscopically, these

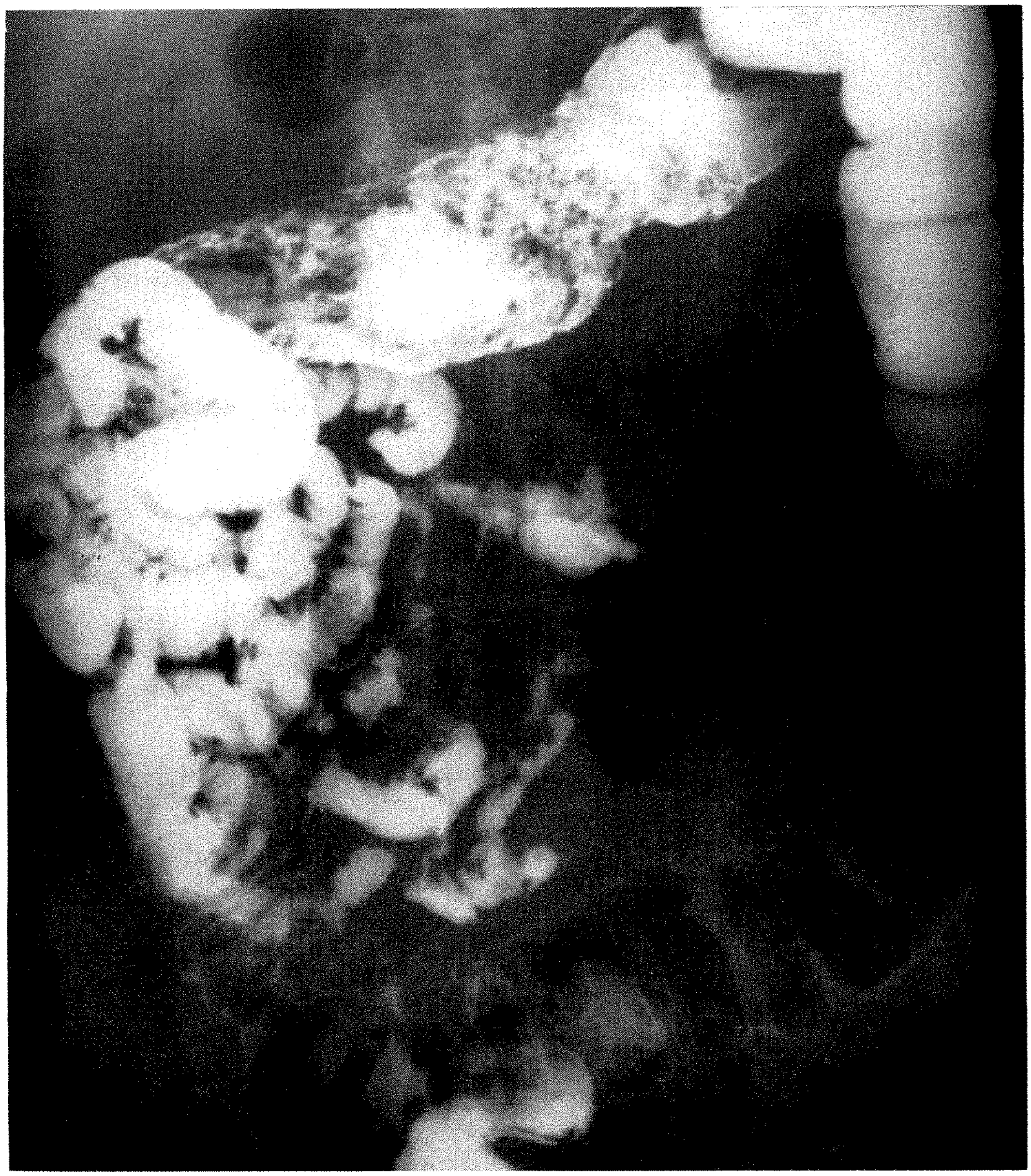

Fig. 4—Case 2, barium enema examination. The cecum and ascending colon are absent. A polypoid tumor mass is present in the transverse colon with no narrowing of the colonic lumen.

were composed of hyperplastic tissue due to extensive mucosal proliferation. A minor inflammatory reaction and granulation tissue were also present. The final pathological diagnosis was recurrent granulomatous ileocolitis with giant pseudopolyposis involving the colon.

COMMENT

Pseudopolyposis is the result of extensive mucosal ulceration which occurs most often in association with severe colonic inflammatory disease.[1] The pseudopolyps represent postinflammatory proliferation of

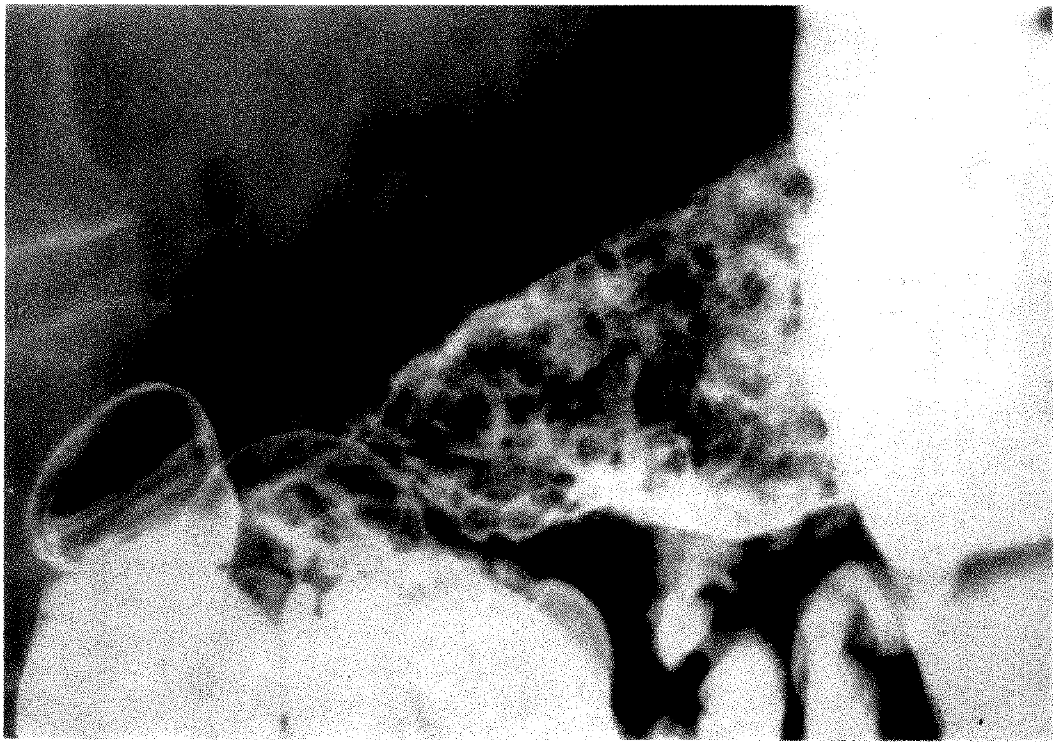

Fig. 5—Spot film made at fluoroscopy with air contrast. There is a villous multinodular mass of pseudopolyps in the transverse colon. A narrow ileocolic anastomosis is evident.

mucosa, islands of surviving epithelium and epithelial granulation tissue.[6] The islands of mucosal inflammation and regeneration are nonspecific and may be seen in a variety of ulcerating colonic diseases including ulcerative colitis,[4] granulomatous colitis, bacterial colitis and necrotizing enterocolitis.[5, 6] The distribution and extent of the pseudopolyps depends on the underlying disorder. Both localized and diffuse forms may occur.

Localized giant pseudopolyposis presumably represents an extreme manifestation of this mucosal proliferative response. The lesion may be present occasionally at the initial presentation of the inflammatory disease of the colon.[3, 5] More frequently, the lesion is first suspected when a mass is palpated[2, 7] or noted radiogically in a patient, without change in symptoms, who is being treated for ulcerative or granulomatous colitis. Obstructive symptoms are infrequent despite the size of the lesion, because the mass is soft, pliable and not associated with any desmoplastic reaction. Case 1 is the first reported example of localized giant pseudopolyposis in a child.

Radiologic features:—Barium enema examination shows a large, localized, polypoid filling defect in the colon which may partially or completely fill the lumen of the bowel. Linear, "finger-like", filiform strands are noted on the surface of the mass. The lesion has the shaggy features of a villous tumor and may be compressable as well as changeable in shape. The transition between the localized pseudopolyps and the more normal mucosa is usually gradual. Other pseudopolyps are often present elsewhere in the colon.

The main diagnostic concern in a patient with inflammatory bowel disease who develops an intraluminal mass is whether the mass is due to carcinoma. A carcinoma that develops in ulcerative colitis is rarely polypoid but is either flat and ulcerated or constricting. Other differential diagnostic considerations include fecal material, lymphosarcoma, colitis cystica profunda, villous adenoma and intussusception.[2,-7-9]

Pathology:—Localized giant pseudopolyposis is a striking reactive response that creates marked polypoid overgrowth of the mucosa. Grossly, there is a focal mass of villous mucosal excrescences. The surface of the mass is often covered with long, filiform projections which measure one or two centimeters in length. There are interconnecting mucosal bridges which extend from the surface of the mass across the lumen of the bowel. Microscopically, these masses are due to proliferation of intact colonic mucosa over a slightly thickened, fibrous stroma. An inflammatory reaction and granulation tissue may be present, but are not prominent. There is no neoplastic transformation in the proliferating mucosa.[2-4, 7-9]

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The Last Page

QUESTIONS IN GASTROENTEROLOGY

MICHAEL RUOFF, M.D., F.A.C.G.*
New York, NY

The Last Page appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page,* again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. CONCERNING GASTROINTESTINAL ENDOSCOPY:
   A. All agree that emergency endoscopy of the upper gastrointestinal tract in the presence of bleeding significantly reduces morbidity, mortality and duration of hospital stay.
   B. When performing ERCP care must be taken to disinfect the inner surfaces of the instruments.
   C. Snare biopsy can reach a depth of 4 mm. with thickened folds and up to a depth of 8 mm. where carcinomatous lesions are suspected.
   D. The mortality rate of endoscopic papillotomy is significantly higher than that seen with surgical transduodenal sphincterotomy.

(Page 534)

2. LASER PHOTOCOAGULATION:
   A. Is effective with a green-blue argon laser as the maximum absorption is in red tissue areas.
   B. Can be used to control bleeding from any sized gastroduodenal vessel.
   C. By charring tissue causes self-limitation of absorbed energy.
   D. Gives maximum coagulation in the submucosa.

(Page 541)

3. THE LOWER ESOPHAGEAL RING (SCHATZKI'S RING):
   A. Is located at the squamocolumnar junction of the distal esophagus.
   B. Frequently causes dysphagia or episodic aphagia with diameters less than 13 mm.
   C. Is frequently associated with reflux.
   D. Is rarely found in females.

(Page 546)

4. STEATORRHEA AFTER PARTIAL GASTRIC RESECTION IS DUE TO:
   A. Accelerated transit time with deficient contact between food mass and mucosa.
   B. Inappropriate timing of the release of bile and pancreatic juice into the small intestine.
   C. Bile salt deconjugation.
   D. Bacterial overgrowth in the proximal small intestine.

(Page 555)

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[*] Assistant Professor of Clinical Medicine, New York University School of Medicine.

5. CONCERNING HBsAg:

   A. Chronic carriage may be due to inherited susceptibility to chronic HBV infection with a simple autosomal recessive trait.

   B. Vertical transmission from carrier mothers is more likely to occur than transmission from carrier fathers.

   C. Hepatocarcinogenesis by HBV is necessarily accompanied by a cirrhotic process.

   D. Host response to the infective agent is of predominant importance in determining the clinical course rather than the viral factors.

   (Page 563)

6. STUDIES OF IMMUNOGLOBULINS A AND M IN PANCREATODUODENAL FLUID REVEAL THAT:

   A. Differences in A/M ratios can be detected between patients with benign diseases.

   B. Ig-A levels rise with pancreatic inflammation.

   C. No significant differences exist between normals, patients with chronic pancreatitis and patients with pancreatic carcinoma.

   D. In pancreatic cancer a fall in Ig-A is associated with a rise in Ig-M.

   (Page 568)

7. •N-BENZOYL-L-TYROSYL-P-AMINO BENZOIC ACID (N-BT-PABA3):

   A. Is a chymotrypsin labile peptide that can be given orally to evaluate exocrine pancreatic function.

   B. Is split into free PABA in the presence of chymotrypsin.

   C. Cannot be used to evaluate pancreatic function in the presence of renal and hepatic dysfunction.

   D. Is a procarcinogen implicated in the pathogenesis of pancreatic carcinoma.

   (Page 577)

8. CONCERNING COMPUTED TOMOGRAPHY AND ABDOMINAL DISEASES:

   A. Loss of the peripancreatic fat plane is a reliable sign denoting the presence of carcinoma of the pancreas.

   B. Fluid in the stomach or intestine may incorrectly suggest a pancreatic abnormality.

   C. The use of contrast agents will improve diagnostic accuracy.

   D. Early studies showed a significant advantage of CT over nuclear scanning and angiography.

   (Page 580)

9. RENAL CELL CARCINOMA IS ASSOCIATED WITH:

   A. Direct bowel invasion or submucosal metastatic implantation.

   B. Hypocalcemia.

   C. Polycythemia.

   D. Fever of unknown etiology.

   (Page 582)

10. IF A SNARE LOOP IS ENTRAPPED WITH POLYP DURING POLYPECTOMY:

    A. The polyp should be severed, blindly if necessary, with the electrosurgical current.

    B. The scope should be removed and another colonoscope passed parallel to the snare.

    C. The patient must be explored.

    D. Applying gentle traction to one of the segments of the wire which protrude from the proximal end may accomplish removal.

    (Page 589)

11. EXTRAHEPATIC OBSTRUCTION OF THE PORTAL VENOUS SYSTEM:

    A. Usually presents with recurrent encephalopathy.

    B. Is most often the result of venous thrombosis.

    C. Rarely presents with sudden unexpected and often massive gastrointestinal bleeding.

    D. Will not cause encephalopathy unless associated with severe liver disease.

    (Page 593)

12. SQUAMOUS CELL CARCINOMA OF THE STOMACH:

A. Can arise from gastric squamous mucosa present on a congenital basis.

B. Has a characteristic radiographic and endoscopic appearance.

C. May develop in acquired squamous mucosa that follows local injury.

D. Lacks the glandular differentiation seen with adenosquamous carcinomas.

(Page 597)

13. THE HEPATIC VEINS HAVE BEEN REPORTED TO BE OCCLUDED BY:

A. Renal adenocarcinoma.

B. Primary and secondary hepatic carcinoma.

C. Leiomyosarcomas.

D. Primary adrenocortical carcinoma.

(Page 600)

14. IN CROHN'S DISEASE OF THE COLON:

A. *Pyoderma gangrenosum* is as common as in ulcerative colitis.

B. Oral mucosal ulcers show polymorphonuclear and eosinophilic infiltration of the *lamina propria* and perivascular deposition of fibrin.

C. Oral mucosal ulcers show focal collections of lymphocytes and perivascular infiltrates of mononuclear cells in the *lamina propria* and submucosa.

D. Oral lesions contain a granuloma in 50% of biopsies.

(Pages 603 and 604)

15. *ASCARIS LUMBRICOIDES:*

A. Is seen in about one-fourth of the world population.

B. Larvae migrate from the intestine to the lungs.

C. Is more commonly found in patients with bronchial asthma than in control patients.

D. Eggs may be confused with fungal spores and pollens encountered in stool examinations.

(Page 606)

16. BLOOD IN THE UPPER GASTROINTESTINAL TRACT OF THE NEWBORN MAY BE DUE TO:

A. Hemorrhagic disease.

B. Esophageal varices.

C. Stress ulcer.

D. Swallowed placental blood.

(Page 608)

17. LOCALIZED GIANT PSEUDOPOLYPOSIS OF THE COLON:

A. Is limited to patients with ulcerative colitis.

B. Commonly causes antegrade obstruction of the large bowel.

C. Represents postinflammatory proliferation of mucosa, islands of surviving epithelium and epithelial granulation tissue.

D. Can be confused with the polypoid carcinomas that commonly develop in ulcerative colitis.

(Page 609)

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

Psychotherapy in Chronic Ulcerative Colitis, 1st edition: by Aaron Karush, M.D., George E. Daniels, M.D., Charles Flood, M.D. and John F. O'Connor, M.D. 148 pages, illustrated. W. B. Saunders, Co., Philadelphia, PA, 1977. Price $13.75.

This book represents the combined experience of 40 years at the Columbia-Presbyterian Medical Center in New York clarifying the complex course and nature of chronic ulcerative colitis from a psychotherapeutic point of view. This book constitutes a comprehensive review of the general course of both ulcerative colitis and Crohn's disease involving the colon with emphasis upon the former. Recent endoscopic studies in this disease are included in an extensive review of the psychosomatic literature on chronic ulcerative colitis. Chapter 3 includes a short comparison of ulcerative and granulomatous colitis. Differences in psychic make-up between the two forms of colonic disease are discussed.

This is followed by a chapter on the psychodynamic predisposition to ulcerative colitis and the process of psychotherapy in this disease is considered. After a detailed consideration of several case histories, a very important final chapter considers both the physiological and psychological response of the patient to removal of the colon. This is particularly important in patients with ileostomies. The development of the internal Kock pouch should lead to changes in the attitude of people to this disease both before and after surgical excision of the colon. This is an interesting book by a group of experts who have devoted many years to the study of psychotherapy in chronic ulcerative colitis and will be of interest to gastroenterologists, internists and surgeons who have a major interest in inflammatory bowel disease.

Adrian J. Greenstein, M.D., F.A.C.G.

Endoscopic Retrograde Pancreaticocholangiography: by H. Anacker, H. D. Weiss and B. Kramann. 123 pages, illustrated. Springer-Verlag New York Inc. Secaucus, NJ, 1977. Price $29.50.

This monograph on ERCP is timely as the rapid development of this radiologic technic over the last five years has lead to this procedure being considered almost routine at some of the major institutions in the United States today. This monograph is small but considers most of the major aspects of this new technic. Following an introductory chapter on intraoperative pancreatography the history of pancreatography is considered in some detail. The technical equipment is then described in detail. Following this the indications, contraindications and complications of this procedure are considered. The interpretation of the normal ERCP is followed by consideration of changes which may be attributed to increasing age. Finally changes related to pathologic lesions of the pancreas and papilla as well as diseases of the biliary tract are described. This is a comprehensive monograph covering in considerable detail all the known anatomic knowledge in relationship to the ductal system of the pancreas and liver. An attempt is made to classify chronic pancreatitis into three stages. Stage 1, slight marginal irregularities in ductal system; Stage 2, ductal irregularities plus involvement of side branches; Stage 3, dilatation of the main pancreatic duct proximal to an area of stenosis and sometimes a chain of lakes effect with multiple areas of stenosis and dilatation. Whether these represent progressive stages of a single clinical entity or simply different manifestations of irregular fibrosis in a diseased gland and ductal system would be difficult to establish. A comparison of this technic with other methods of studying the pancreas is made and analyzed statistically. Thus the limitations of this technic are considered. This book will be of value to gastroenterologists, internists as well as surgeons involved in the study and treatment of pancreatic disease. The rapid advances of our understanding of the anatomic changes that occur within the ductal system of the pancreas and the associated pathologic entities, are in no small measure due to the recent development of this technic together with the considerable improvement in recent years and months of ultrasonic scanning of the gland and of computerized axial tomography.

Adrian J. Greenstein, M.D., F.A.C.G.

Gastrointestinal Bleeding, Diagnosis and Management: by John A. Balint, M.B., F.A.C.G., I. James Sarfeh, M.D. and Martin B. Fried, M.D. 101 pages, illustrated, John Wiley & Sons, Inc., New York, NY, 1977. Price $14.00.

This book is one volume in the series of "Clinical Gastroenterology Monographs". It covers, in sufficient detail, current information on the pathophysiology, diagnosis and therapy of gastrointestinal bleeding.

The pathophysiological concepts underlying gastrointestinal bleeding and their clinical implications are extensively reviewed with clarity and precision.

Highly recommended to gastroenterologists and general surgeons.

Demetrius Pertsemlidis, M.D., F.A.C.G.

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Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
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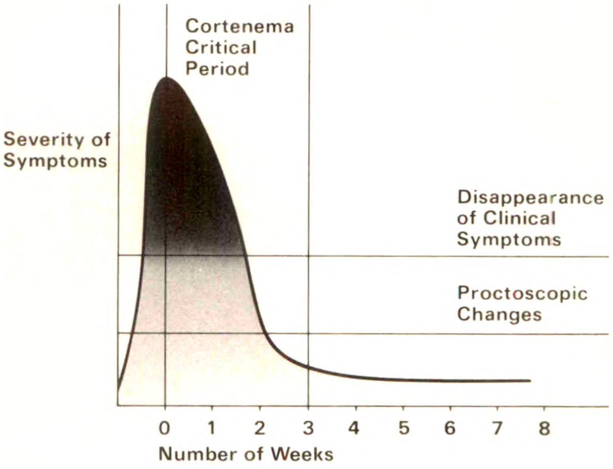

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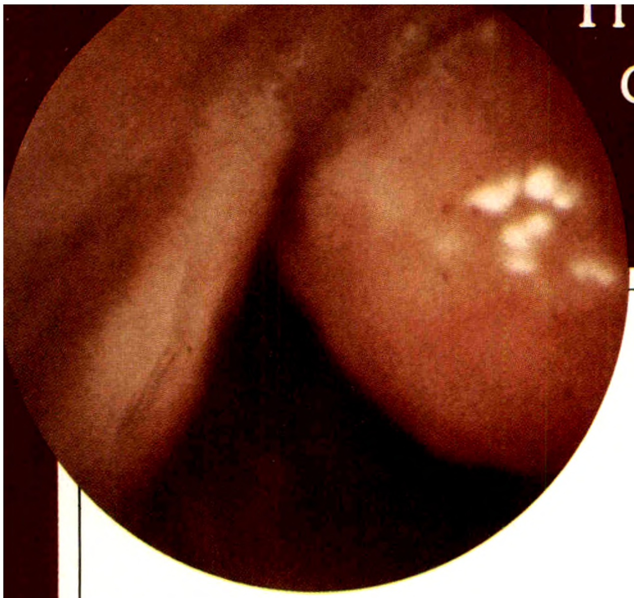

The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing.
X-ray studies are inconclusive.

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Esophagoscopy was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

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Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
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Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
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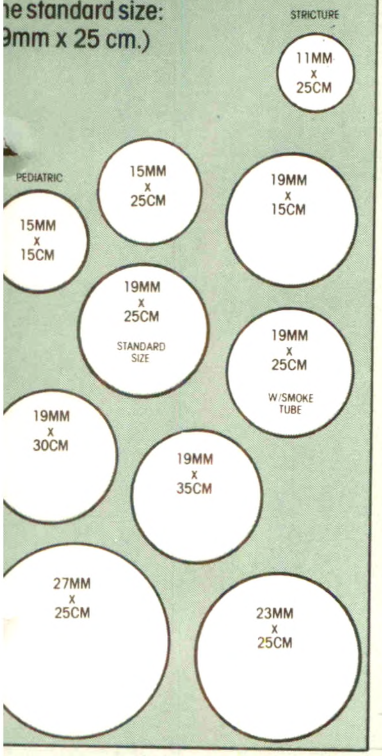

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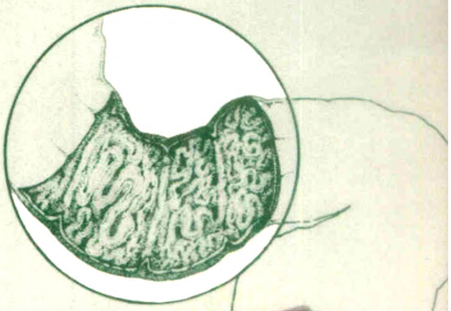

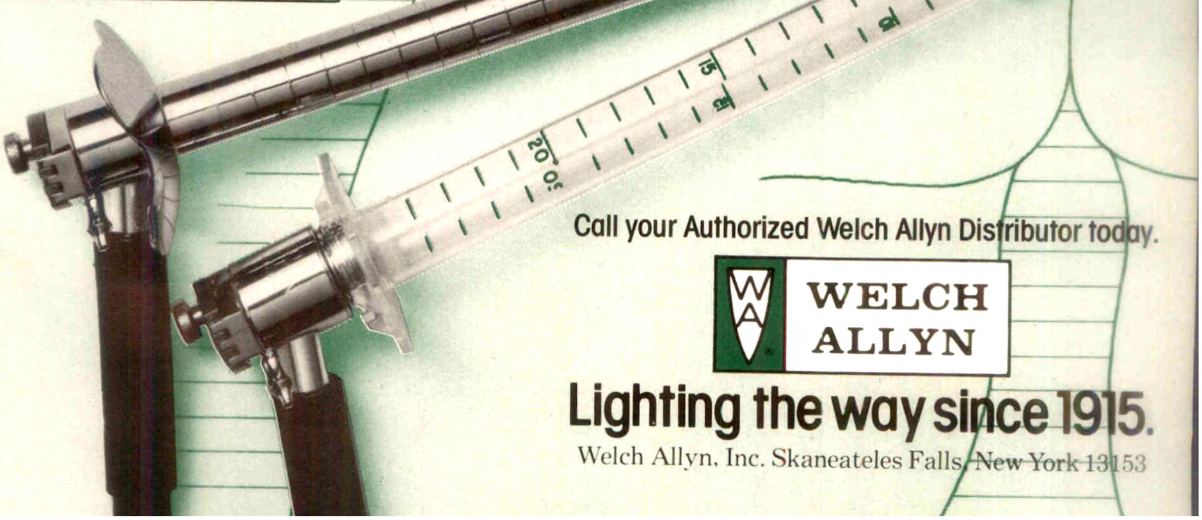

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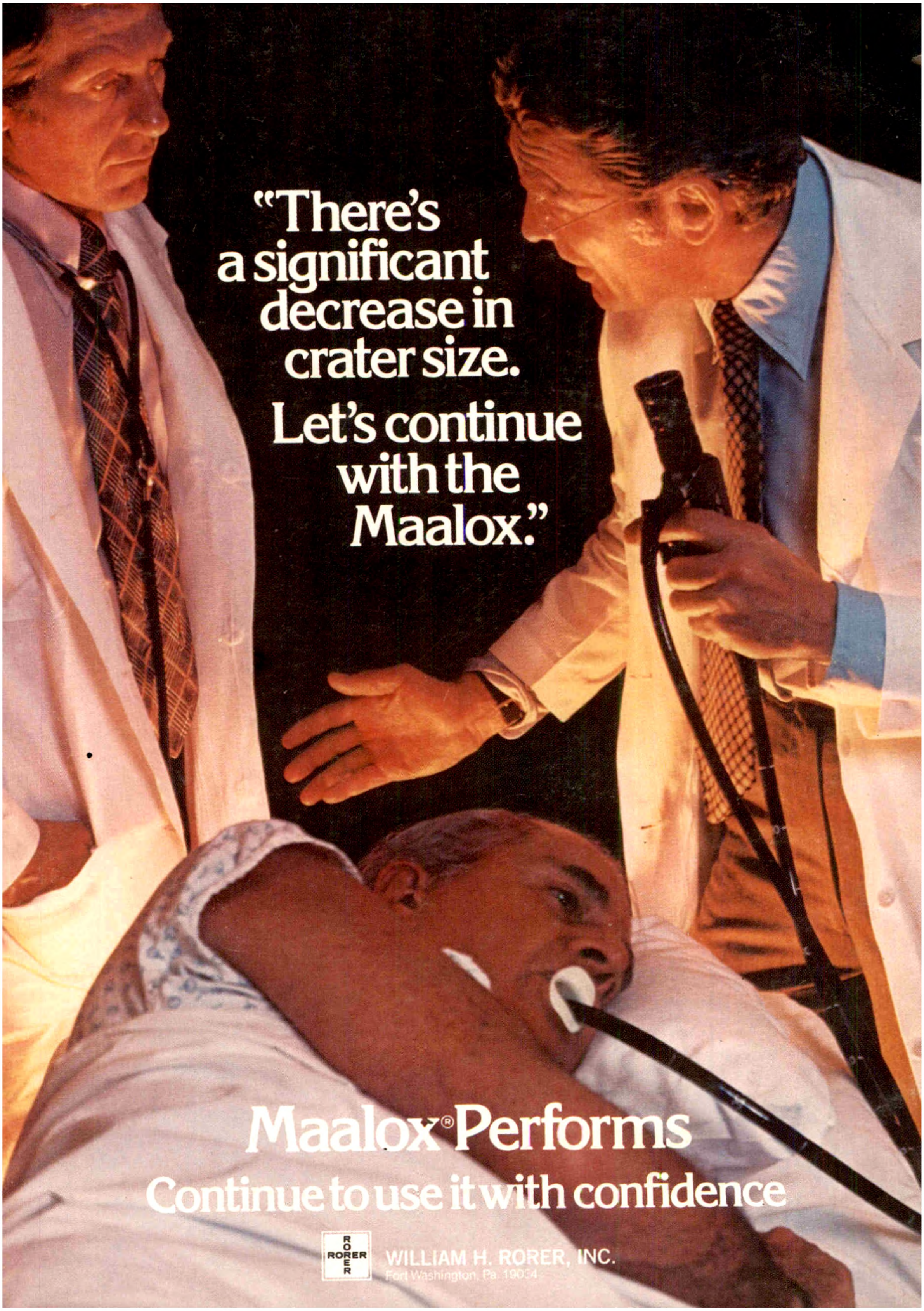
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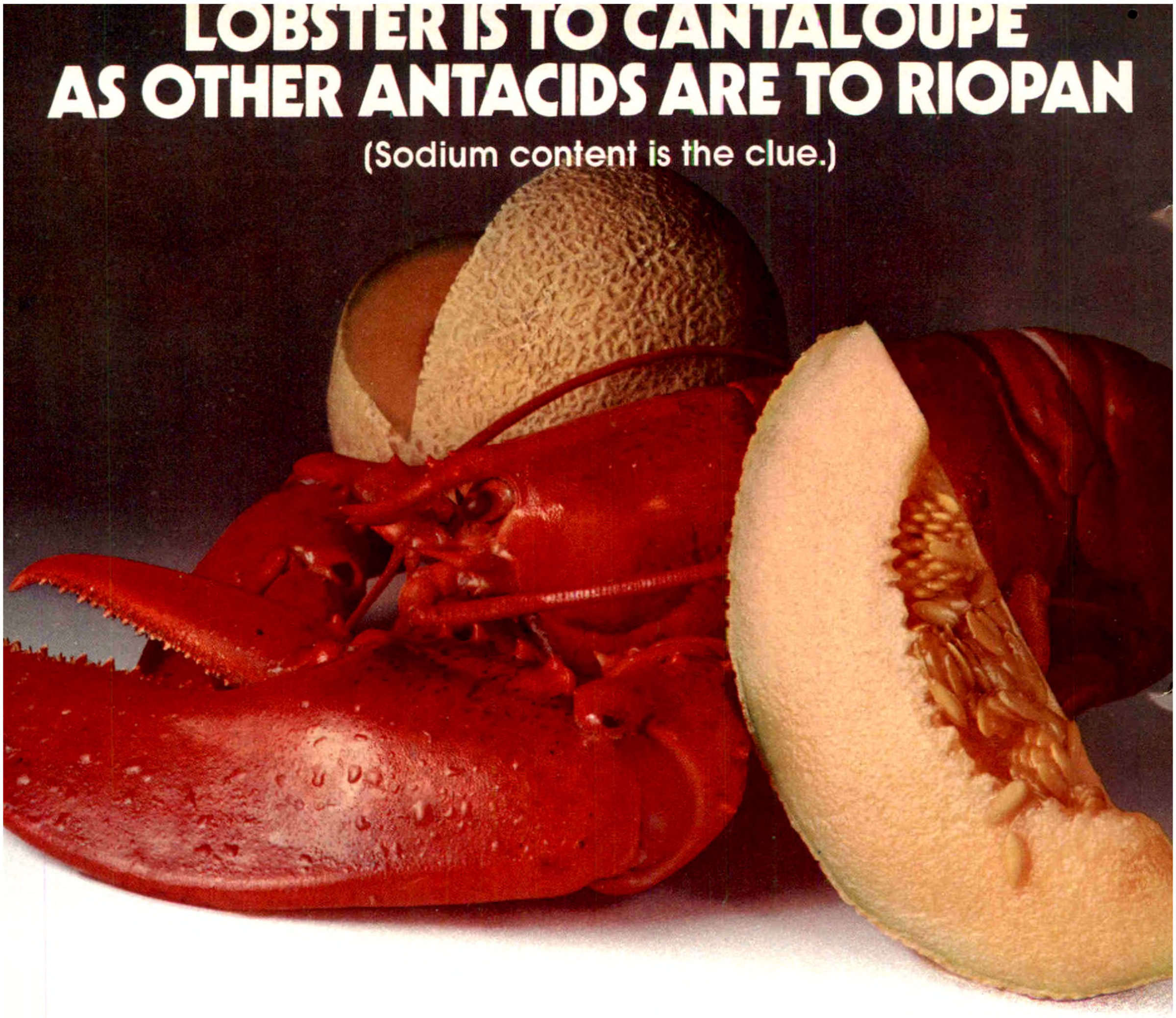

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2. Penna, R.P., et al. (eds.): Handbook of Nonprescription Drugs, Washington, D.C., American Pharm. Assn., Ed. 5, 1977, pp. 13-17.
3. Penna, R.P.: Antacids, in Handbook of Nonprescription Drugs, Washington, D.C., American Pharm. Assn., 1973 Ed., pp. 12, 14.
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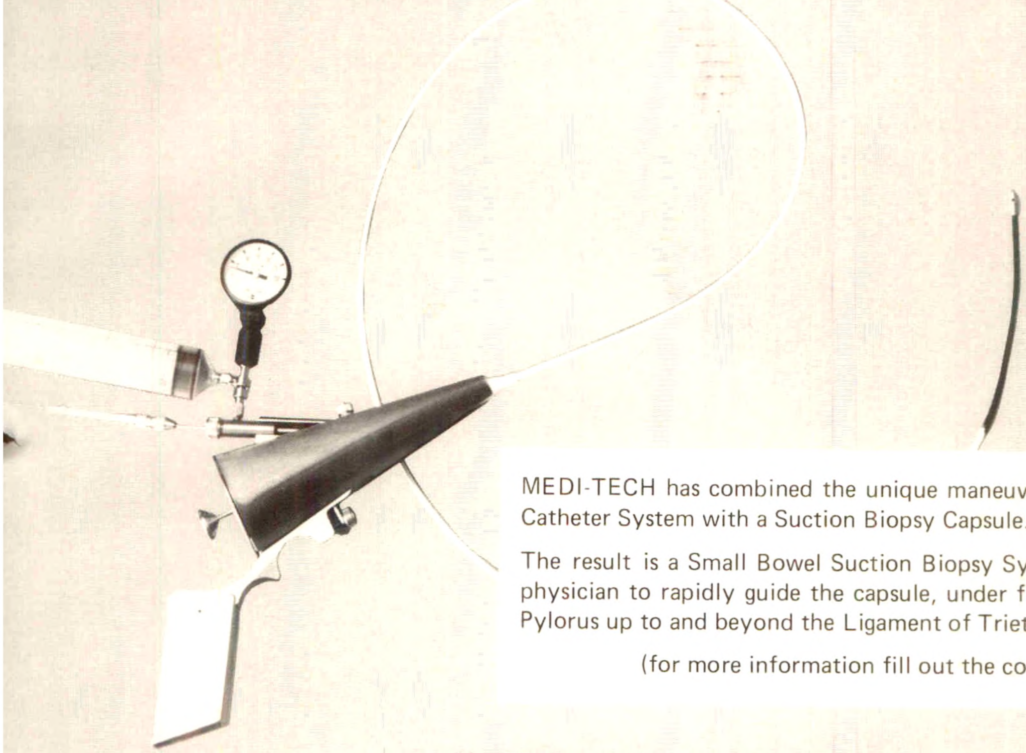

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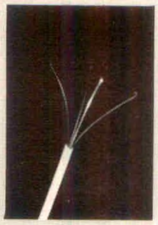

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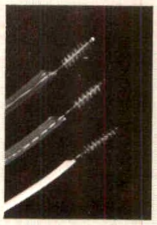

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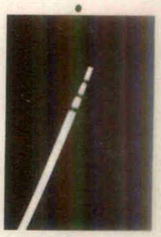

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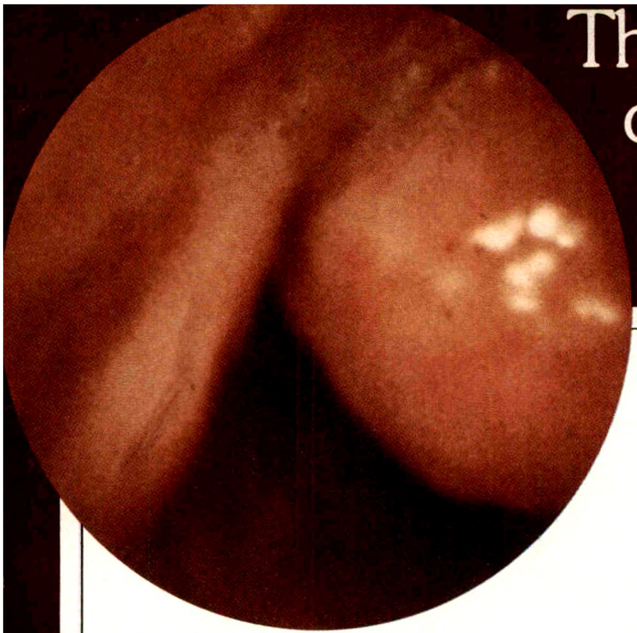

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1 Only Librax provides the specific antianxiety action of Librium® (chlordiazepoxide HCl), in addition to the antisecretory-antispasmodic actions of Quarzan® (clidinium Br)—both original developments of Roche research.

2 Librax seldom impairs mental acuity or performance when given in proper dosage. However, as with all preparations containing CNS-acting agents, patients should be cautioned against hazardous occupations requiring complete mental alertness.

3 Flexibility of dosage helps meet varying requirements: 1 or 2 capsules three or four times daily, before meals and at bedtime.

4 The convenience and economy of a single Rx help sustain patient compliance, while providing relief of both emotional and somatic symptoms.

A distinctive antianxiety-antispasmodic agent

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

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***Librax has been evaluated as possibly effective for this indication. Please see brief summary of prescribing information on following page.**

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, singly and in trays of 10.

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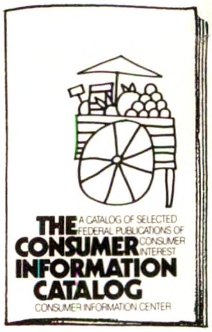
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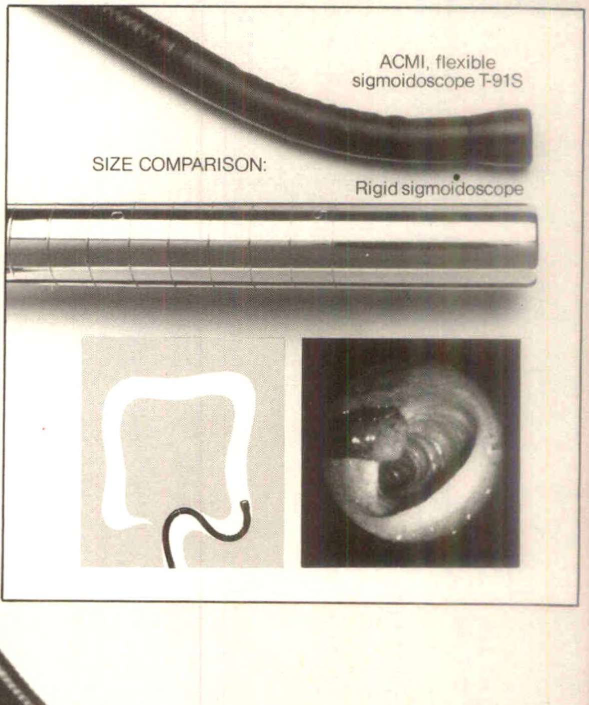

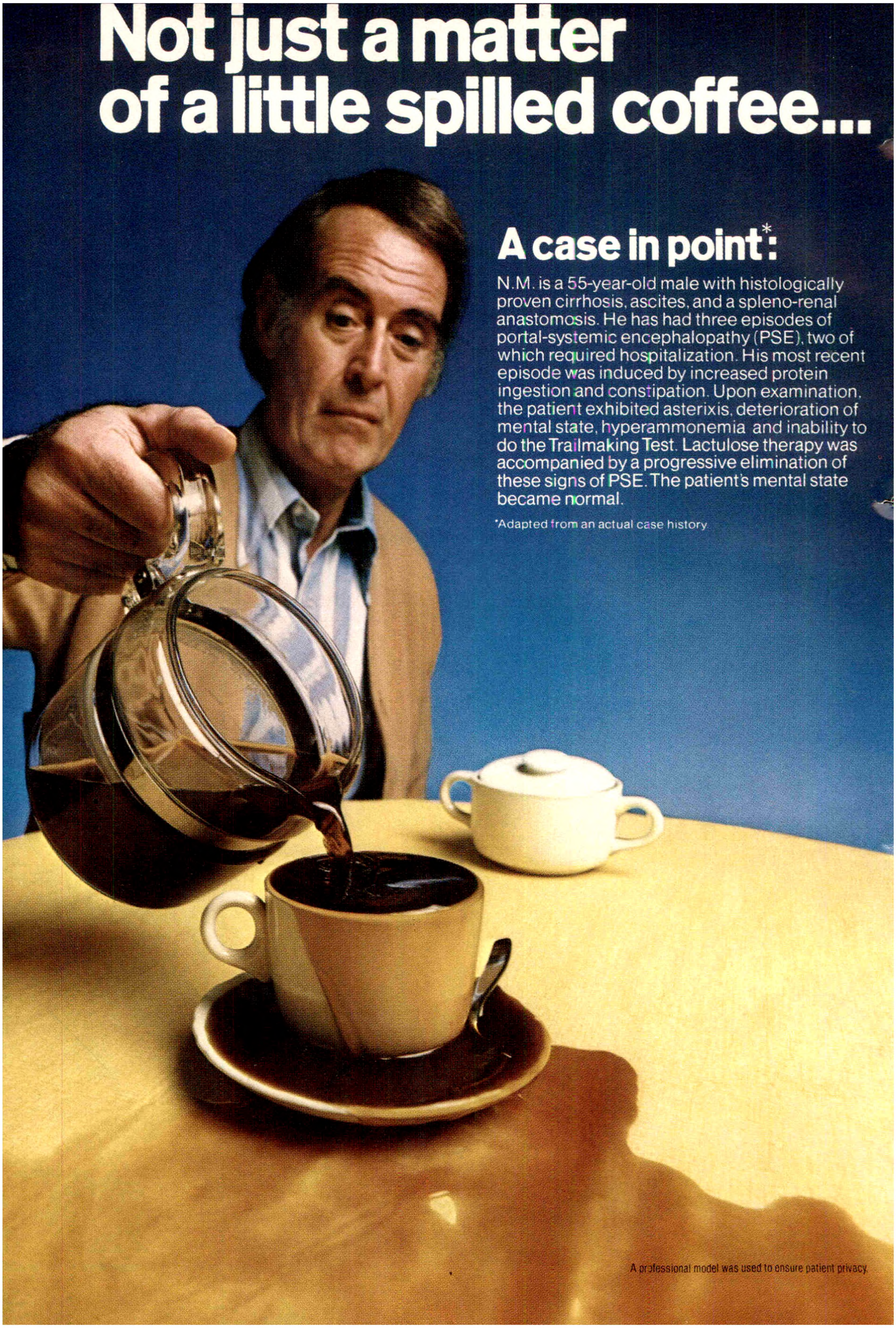
Not just a matter of a little spilled coffee...

A case in point*:

N.M. is a 55-year-old male with histologically proven cirrhosis, ascites, and a spleno-renal anastomosis. He has had three episodes of portal-systemic encephalopathy (PSE), two of which required hospitalization. His most recent episode was induced by increased protein ingestion and constipation. Upon examination, the patient exhibited asterixis, deterioration of mental state, hyperammonemia and inability to do the Trailmaking Test. Lactulose therapy was accompanied by a progressive elimination of these signs of PSE. The patient's mental state became normal.

*Adapted from an actual case history.

A professional model was used to ensure patient privacy.

...this is portal-systemic encephalopathy (PSE)–

(Also called Hepatic Encephalopathy, Hepatic Coma.)

–a common complication of chronic liver disease.

Suspect PSE in every patient with cirrhosis.

Common early symptoms

- irritability
- euphoria
- lack of concern for others
- inappropriate behavior
- faraway look
- inversion of sleep pattern

Results of recent investigations of PSE

- Two-thirds of cirrhotic patients with portal hypertension who appeared mentally normal by conventional assessment revealed impairment of cerebral function on psychomotor testing. This dysfunction was in the same range as that in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

Treat PSE with Cephulac (lactulose) Syrup

- relieves PSE in 75% of episodes
- acts without serious adverse reactions
- lowers blood ammonia levels
- improves EEG and mental state
- permits more normal dietary protein intake
- provides an easy-to-manage means of long-term therapy

Cephulac®
(lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

for the prevention and treatment of PSE in your patients with chronic liver disease

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MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc
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Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose di

WARNINGS: *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

References:

1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.
2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and noncirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.
3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 72:1119, 1977.

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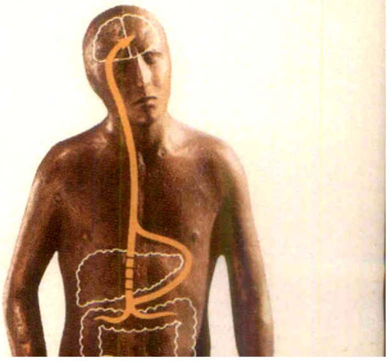

Avoid U.C. flare-up over the long haul

4½ times greater relapse rate for non-Azulfidine-treated patients revealed in a double-blind study.[1]

Your patients need your guidance to help prevent recurrence of ulcerative colitis. They may not be aware that U.C. with all its pain and discomfort is a chronic disease. Several investigators[2-6] have shown that the best way to control relapse is to medicate over the long-term with Azulfidine (sulfasalazine, N.F.). Further proof is contained in the double-blind "Truelove" study.[1*]

Ulcerative colitis patients were symptom-free at the start of this controlled study. All had been maintained on Azulfidine for from one to over five years. During the six-month trial, more than 54% of the placebo group suffered relapse—a rate 4½ times greater than the 12.1% who showed a recurrence of symptoms in the Azulfidine-treated group! The therapeutic action of Azulfidine was credited with the striking difference in these figures.

The only side effects among the study group were two cases of nausea and one of headache. (These symptoms ceased without a change in dosage when patients returned to open therapy.)

The authors concluded that maintenance treatment of ulcerative colitis with Azulfidine should be continued indefinitely unless contraindicated by side effects. Observe patients carefully, since in many cases adjustment of dosage will control side effects (see Prescribing Information). Azulfidine is also available in enteric-coated EN-tab® tablet form for those patients susceptible to gastric upset.

Over the long haul the best preventative is the proven safety of continuing maintenance treatment.

*Reprint available from Pharmacia.

AZULFIDINE®
(sulfasalazine, N.F.)

Simulated flares on a pipeline intended to represent acute exacerbation of chronic ulcerative colitis.

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AZULFIDINE®
(sulfasalazine, N.F.)
Tablets and EN-tabs®

INDICATIONS: AZULFIDINE (sulfasalazine, N.F.) is indicated in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis. AZULFIDINE EN-tabs are particularly indicated in patients who experience gastrointestinal intolerance after the first few doses of the drug, when such intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites and in those for whom a reduction in dosage does not alleviate the gastrointestinal effects.

CONTRAINDICATIONS: Hypersensitivity to sulfonamides or salicylates. In infants under 2 years. Intestinal and urinary obstruction. Pregnancy at term and during the nursing period. In patients with porphyria.

WARNINGS: The safe use of sulfonamides in pregnancy has not been established. Evaluate benefit to risk carefully when giving sulfonamides during pregnancy, especially at term, since kernicterus may be produced in the newborn. The teratogenic potential of most sulfonamides has not been thoroughly investigated in any species and a significant increase of cleft palate and other bony abnormalities has been observed when certain sulfonamides were given orally to pregnant rats and mice at 7 to 25 times the human therapeutic dose.

Deaths associated with the administration of AZULFIDINE (sulfasalazine, N.F.) have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and CNS changes and fibrosing alveolitis.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders.

Complete blood counts as well as urinalysis with microscopic examination should be done frequently.

PRECAUTIONS: Administer with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia.

Maintain adequate fluid intake to prevent crystalluria and stone formation.

ADVERSE REACTIONS: Adverse reactions have been observed in 5 to 55% of patients included in clinical studies reported in the literature. Experience suggests that with daily dosages of 4 g or more, adverse reactions tend to increase. The most common adverse reactions associated with AZULFIDINE therapy are anorexia, nausea, vomiting, and gastric distress. The following adverse reactions have been reported to occur during therapy with AZULFIDINE.

Blood dyscrasias: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, Heinz Body anemia, purpura, hypoprothrombinemia, "cyanosis," and methemoglobinemia.

Hypersensitivity reactions: Generalized skin eruptions, erythema multiforme (Stevens-Johnson syndrome), parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, pruritus, urticaria, photosensitization, anaphylaxis, serum sickness syndrome, chills, drug fever, periorbital edema, conjunctival and scleral injection, arthralgia, transient pulmonary changes with eosinophilia and decreased pulmonary function, allergic myocarditis, polyarteritis nodosa, and L.E. phenomenon.

Gastrointestinal reactions: Anorexia, nausea, emesis, abdominal pains, diarrhea, bloody diarrhea, impaired folic acid and digoxin absorption, stomatitis, pancreatitis, and hepatitis.

CNS reactions: Headache, vertigo, tinnitus, hearing loss, peripheral neuropathy, transient lesions of posterior spinal column, transverse myelitis, ataxia, convulsions, insomnia, mental depression, hallucinations and drowsiness.

Renal reactions: Crystalluria, hematuria, proteinuria, and nephrotic syndrome. Toxic nephrosis with oliguria and anuria.

Incidents of alopecia and reduction in sperm count and viability have also been reported.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross sensitivity may exist with these agents.

AZULFIDINE (sulfasalazine, N.F.) produces an orange-yellow color when the urine is alkaline. Similar discoloration of the skin has also been reported.

SUPPLIED: Tablets and EN-tabs (enteric-coated) 0.5 gm, in bottles of 100 and 500. Also available as Azulfidine Unit Dose in boxes of 100's and 1000's.

IMPORTANT: See full prescribing information before administering AZULFIDINE.

References:
1. Dissanayake, A.S. and Truelove, S.C.: Gut 14:923-926, Dec. 1973.
2. Bargen, J.A.: Amer. Surg. 28:630-637, Sept. 1962.
3. Hightower, N.C., Jr., et al.: Amer. J. Digest. Dis. 3:722-733, 861-876, 931-941, Oct., Nov., Dec. 1958.
4. Roth, J.L.A.: Chapter 69, in Bockus, H. (ed.): Gastroenterology, Vol. II, W.B. Saunders Company.
5. Riis, P., et al.: Scand. J. Gastroenterol. 8:71-74, 1973.
6. Goldstein, F. and Thornton, J.J.: Consultant 14:96-103, July 1974.

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MEETINGS OF INTEREST

43rd Annual Convention, American College of Gastroenterology, The Marriott, Denver, Colo., 24-27 September 1978.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, The Marriott, Denver, Colo., 28-30 September 1978.

One Day of Gastroenterology, Postgraduate Course co-sponsored by the American College of Gastroenterology, the Southern Medical Association. Georgia World Congress Center, Atlanta, Ga., 11 November 1978.

in irritable colon*

When stress makes waves for the spasm reactor...

A normal reaction to emotional stress is a marked increase in both the strength and frequency of wave-like contractions of colonic motility.[1] However, in the patient with irritable bowel syndrome, this psychovisceral reaction is of greater intensity and duration than normal.[2]

The result can be G.I. spasm.

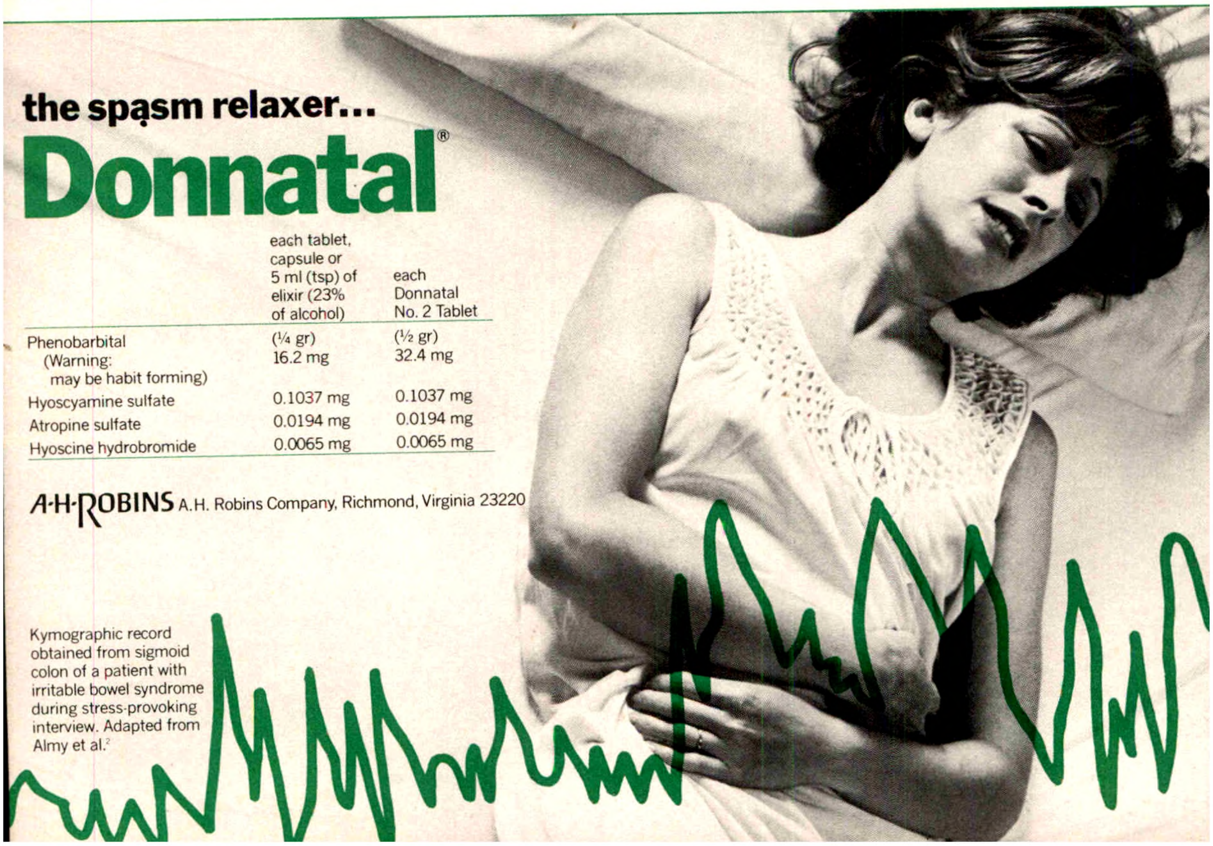
When spasm and pain associated with irritable bowel syndrome call for treatment beyond your counseling and reassurance, Donnatal may prove to be a helpful adjunct. The smooth central sedation and prompt peripheral antispasmodic/anticholinergic action of Donnatal may provide this symptomatic relief necessary to help calm the waves ...and quell the spasm.

References: 1. Almy, T.P., Kern, F., and Tulin, M.: Alterations in colonic function in man under stress. II: Experimental production of sigmoid spasm in healthy persons. *Gastroenterology* 12(3):425-436, 1949. **2.** Almy, T.P., Hinkle, L.E., Berle, B., et al.: Alterations in colonic function in man under stress. III: Experimental production of sigmoid spasm in patients with spastic constipation. *Gastroenterology* 12(3):437-449, 1949.

*Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindicated in patients with glaucoma, renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy), or a hypersensitivity to any of the ingredients. Blurred vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur at higher dosage levels, rarely at the usual dosage.



the spasm relaxer...

Donnatal®

	each tablet, capsule or 5 ml (tsp) of elixir (23% of alcohol)	each Donnatal No. 2 Tablet
Phenobarbital (Warning: may be habit forming)	(¼ gr) 16.2 mg	(½ gr) 32.4 mg
Hyoscyamine sulfate	0.1037 mg	0.1037 mg
Atropine sulfate	0.0194 mg	0.0194 mg
Hyoscine hydrobromide	0.0065 mg	0.0065 mg

A·H·ROBINS A.H. Robins Company, Richmond, Virginia 23220

Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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VOLUME 69 JUNE, 1978 NUMBER 6

Peritoneoscopy: An Alternative Approach to Unresolved Intra-abdominal Disease*

JEAN W. SALEH, M.D.
New York, NY

Peritoneoscopy was performed in 49 patients with ill-defined intra-abdominal disease. The patients were classified into categories including inconclusive liver scans, jaundice, ascites, abdominal mass and staging for Hodgkin's disease. Visual evaluation of lesions and directed biopsies led to the correct diagnosis in 87% of the cases. In experienced hands, peritoneoscopy is a safe and useful technic and should be considered strongly in obscure intra-abdominal diseases.

INTRODUCTION

Increasingly, peritoneoscopy is becoming a procedure of choice for the diagnosis of intra-abdominal diseases.[1] The safety and usefulness of this technic have extended its use beyond the scope of liver diseases including peritoneal seeding and metastases, staging for Hodgkin's disease,[2] jaundice, ascites and a variety of surgical disorders.[3, 4] The direct visualization of lesions and directed biopsies have made the technic of paramount importance for definitive diagnosis and possibly treatment, namely for the Fitz-Hugh Curtis syndrome[5] and tubal ligation. Blind liver biopsy, endoscopic retrograde cholangiopancreatography, liver scintiscanning, selective arteriography and ultrasound, are all well established technics with their values and limitations. Nevertheless, peritoneoscopy represents a valuable alternative, especially when the intra-abdominal disease remains obscure, when other diagnostic technics have failed, when it is important to consider or•avoid laparotomy and when direct vision of the lesion and tissue diagnosis become mandatory.

The purpose of this paper is to present data showing that in unresolved intra-abdominal diseases, peritoneoscopy with directed biopsies is an important adjunct to our modern armamentarium.

PATIENTS AND METHODS

Forty-nine patients with unresolved intra-abdominal diseases encompassing inconclusive liver scans (29), jaundice (5), ill-defined abdominal mass (7), ascites (6) and staging for Hodgkin's disease (2), were referred to our Gastrointestinal Unit for

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[*] Read before the 42nd Annual Convention of the American College of Gastroenterology, New Orleans, LA, 24, 25, 26 October 1977.

From the Division of Gastroenterology, Department of Medicine, St. Luke's Hospital Center, Columbia University, College of Physicians and Surgeons.

TABLE I

CATEGORIES OF THE UNRESOLVED INTRA-ABDOMINAL DISEASES STUDIED BY PERITONEOSCOPY

	No. of patients
Inconclusive liver scans	29
Jaundice	5
Ill-defined abdominal mass	7
Ascites	6
Staging for Hodgkin's disease	2
Total	49

TABLE II

RESULTS OF PERITONEOSCOPY IN PATIENTS WITH INCONCLUSIVE LIVER SCANS

	No. of patients
Perihepatitis with fibrosis	3
Micronodular cirrhosis	8
Macronodular cirrhosis	1
Hepatitis	2
Fatty infiltration	2
Metastatic liver disease	5
Normal findings	4
Positive diagnosis	25
No diagnosis (diffuse intra-abdominal adhesions)	4
Total	29

peritoneoscopy and directed biopsies. All patients were thoroughly evaluated and their charts carefully searched for contraindications. Prothrombin time and platelet counts were obtained on all patients 24 hours prior to the examination. A three-second above control for the prothrombin time and a platelet count over 70,000 were considered reasonable risks to undertake the procedure. Peritoneoscopy was not performed in patients with recent myocardial infarction, acute surgical abdomen, severe chronic obstructive lung disease or blood dyscrasias. These disorders are considered contraindications to the procedure.

The procedure was explained in detail to all patients in order to prevent apprehension and insure full cooperation. In each case, a signed consent was obtained. Patients were fasted 12 hours prior to the examination and they were given, as premedication, 30 minutes before the test, atropine 0.4 mg. and diazepam 10 mg. intramuscularly.

The Wolf operating peritoneoscope No. 4937 was used alternating with the Wolf flash photolaparoscope No. 4317C adapted to an electric flash generator No. 3329. Biopsies were obtained through the operating scope using the needle or the forceps, or through another puncture using the Menghini needle directed to the lesion under constant vision.

After thorough cleansing of the abdominal skin with a mixture of alcohol and iodine or betadine, pneumoperitoneum was induced using a hand bulb or CO_2 pump. A thin Foures needle with lateral holes was introduced after local anesthesia with 1% xylocaine, in the external portion of a line extending from the umbilicus to the anterosuperior iliac crest. Once the abdominal distention was symmetrical and hence considered satisfactory, a small incision was made 2 cm. below the umbilicus after local anesthesia. The trocar was then introduced followed by the peritoneoscope and the examination was begun.

RESULTS

The overall indications for peritoneoscopy are shown in Table I. In the 29 patients with inconclusive liver scans, most of the scan reports described hepatomegaly

TABLE III

Results of Peritoneoscopy in Patients with Jaundice of Undetermined Origin

	No. of patients
Cancer, head of pancreas	2
Choledocholithiasis	1
Cancer, *porta hepatis*	1
Cancer, gallbladder extending to common bile duct	1
Total	5

TABLE IV

Results of Peritoneoscopy in Patients with Ill-defined Intra-abdominal Mass

	No. of patients
Lipoma	1
Cancer, large omentum	2
Cirrhosis with left hepatomegaly	1
Left lobe with metastases	1
Congestive liver disease	1
Positive diagnosis	6
No diagnosis (extensive abdominal scarring)	1
Total	7

with multiple filling defects, heterogenous uptake, single or multiple silent areas together with inconsistent or negative blind liver biopsies. In contrast, in the same patients subjected to peritoneoscopy, as shown in Table II, perihepatitis with capsular inflammation together with moderate fibrosis and hepatic adhesions were seen in three patients, micronodular cirrhosis in eight patients and postnecrotic cirrhosis in one patient. Hepatitis with its characteristic redness and swelling of the liver with blunting of the edges was discovered in two cases and fatty infiltration with enlargement of the liver, yellowish discoloration and doughy consistency in two others. In five patients, both lobes of the liver were covered with white, hard, umbilicated nodules, characteristic of metastases from primary gastrointestinal or pancreatic carcinoma. In four patients the size, color and consistency of the liver were found to be within normal limits. All these findings were corroborated by directed liver biopsies. Finally in four patients, extensive intra-abdominal adhesions secondary to previous surgery or peritoneal irritation or inflammation precluded an adequate examination and diagnosis.

In the five patients with undetermined jaundiced (Table III), biliary obstruction was highly suspected clinically. In two patients, a dark green liver with grossly distended, translucent and hypervascular gallbladder was strongly suggestive of carcinoma of the head of the pancreas. In one case, the gallbladder was distended with a thick whitish wall but was no longer translucent and hypervascular. These findings together with patchy green liver are pathognomonic of choledocolithiasis. In another patient, the gallbladder was found to be completely collapsed, maintaining its fine vascularization and thickness while the liver was diffusely green with inflammation of Glisson's capsule which was covered by worm like linear dilatation of the bile ducts known as *vasa aberrantia.* These lesions are suggestive of carcinoma of the *porta hepatis.* Finally in one patient with a small, whitish and ligneous gallbladder together with inflammation and adhesions in the cholecystic bed, carcinoma of the gallbladder was strongly suspected. In this case the extension of the carcinoma to the common bile duct was presumed since there was hepatomegaly with diffuse greenish

TABLE V

Results of Peritoneoscopy in Patients with Ascites

	No. of patients
Peritoneal tuberculosis	2
Carcinoma peritoneum	2
Micronodular cirrhosis & hepatoma	1
Positive diagnosis	5
No diagnosis (massive ascites)	1
Total	6

discoloration. These diagnoses were all confirmed by laparatomy.

In seven patients with ill-defined intra-abdominal mass (Table IV), a large parietal lipoma was seen in one patient and in two patients, an intra-abdominal carcinoma with diffuse extension to the large omentum, anarchic growth, friability, moderate ascites and adhesions to the parietal peritoneum was discovered. In another patient, the intra-abdominal mass consisted of large left hepatomegaly with over all cirrhosis and portal hypertension. One patient had left lobe metastases, typically umbilicated most likely secondary to a gastrointestinal carcinoma. In another patient the liver was grossly enlarged, hyperemic with punctate phlyctenular white nodules highly characteristic of congestive liver disease.[6] These findings were verified by directed biopsies. Finally in one patient, extensive abdominal scarring, with its multiple corrolary intra-abdominal adhesions, prevented good visualization despite two attempts.

In six patients with ascites (Table V) and inconclusive laboratory and clinical findings, peritoneoscopy disclosed after fluid retrieval two cases of peritoneal tuberculosis with its characteristic white millet seed dissemination and two carcinomas of the peritoneum with unknown primary. In one patient micronodular cirrhosis was found with hepatoma. These diagnoses were confirmed by needle or forceps biopsies. Massive ascites in one case precluded good examination.

Two patients with known Hodgkin's disease underwent peritoneoscopy for intra-abdominal staging. In the two cases, there was no involvement of the liver or the spleen. These findings were confirmed by laparotomy.

The only incident encountered in our series was a subcutaneous emphysema in an obese patient occurring two hours after the procedure. This occurrence resolved spontaneously the following day.

COMMENT

These data clearly show that in unresolved intra-abdominal disease, peritoneoscopy may be an important adjunct in reaching the final diagnosis. The procedure allows not only a direct examination of the lesions but also permits, when doubt exists, directed biopsies under constant observation. The need for a simple technic of celomic investigation was felt around the turn of the century when both Kelling[7] and Jacobeus[8] tried independently to answer these questions, resorting to a small abdominal incision rather than to extensive and, at times, unnecessary laparotomy. Following many years of desuetude due to early imperfections and incidents, peritoneoscopy has become a necessary procedure in any comprehensive program. Its impact lies mostly in the differential diagnosis of jaundice as outlined carefully by the "chromo-diagnosis" of Kalk[9] and of Caroli[10] and in tissue diagnosis. Similar to other technics, however, it has its own limitations, those prescribed by the clinical and laboratory status of the patient and those encountered during the examination, namely extensive adhesions, gross ascites, or yet undefined endoscopic manifestations of an illness. In the latter instance, precise and directed biopsies may resolve the dilemma. Liver diseases or any lesions surfacing on this organ, are readily diagnosed as well as the multiple and subtle presentations of the gallbladder in various diseases. Regional lymphatic and venous compressions secondary to pancreatic diseases[11] are well-known manifestations as are the indirect involvements of the liver and the gallbladder. Spleen manifestations of systemic disease or lymphoma are well outlined and peritoneal, omental and intestinal lesions are all well within the reach of the endoscope and the forceps.

Peritoneoscopy does not pretend to supplant all other well established diagnostic technics. It offers, however, in experienced hands, a simple, safe and effective alternative, to be strongly considered in ill-defined intra-abdominal diseases.

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Crohn's Disease in Barrett's Esophagus

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A patient with regional ileitis (Crohn's disease) developed a benign esophageal stricture. He had no history of heartburn or other symptoms of reflux esophagitis. The diagnosis of Crohn's disease was suspected but could not be proved preoperatively. The surgically resected esophagus showed the gross and microscopic features of Crohn's disease. Barrett's esophageal mucosa was also found in the resected esophagus. Postoperatively, the patient developed a fistula at the esophagogastrostomy site.

Crohn's esophagitis has been reported in 15 patients but none had Barrett's esophagus. We believe our patient reported here is the first case with Crohn's disease and Barrett's esophagus.

Crohn's disease was originally described as an idiopathic benign inflammatory disease of the terminal ileum.[1] Similar histopathological lesions were subsequently described in other parts of the alimentary tract (AT).[2-6] Although the disease can be seen in any part of the AT, involvement of the esophagus is rare.[7-16] Furthermore, the diagnosis in many of the reported cases was not adequately documented. In fact, the existence of Crohn's esophagitis as a disease entity has been questioned.[17]

We saw a patient with a histopathological diagnosis of regional enteritis who developed a benign esophageal stricture. The gross and histopathological findings of the resected esophagus showed features compatible with those seen in Crohn's disease. We also found Barrett's esophageal mucosa in the same specimen. Since the combination of Crohn's disease and Barrett's esophagus has not been reported previously, we describe here our patient and review 15 previously reported cases of Crohn's esophagitis.

CASE REPORT

J. L., a 52-year old white male was admitted to Strong Memorial Hospital with severe dysphagia, weight loss and a draining sinus in his right flank, for the last six months.

He had intermittent diarrhea and back pain since the age of 30. In 1959, x-rays of his spine showed ankylosing spondylitis. In February, 1961, he developed intestinal obstruction and perforation. At laparotomy, a large mass (12 cm. × 8 cm.) at the terminal ileum was found. The histology of the resected small bowel showed features of regional enteritis (Fig. 1). In 1964, he underwent surgery for an anal fistula. Microscopically, the fistula showed fibrosis and nonspecific chronic inflammation with a few multinucleated giant cells.

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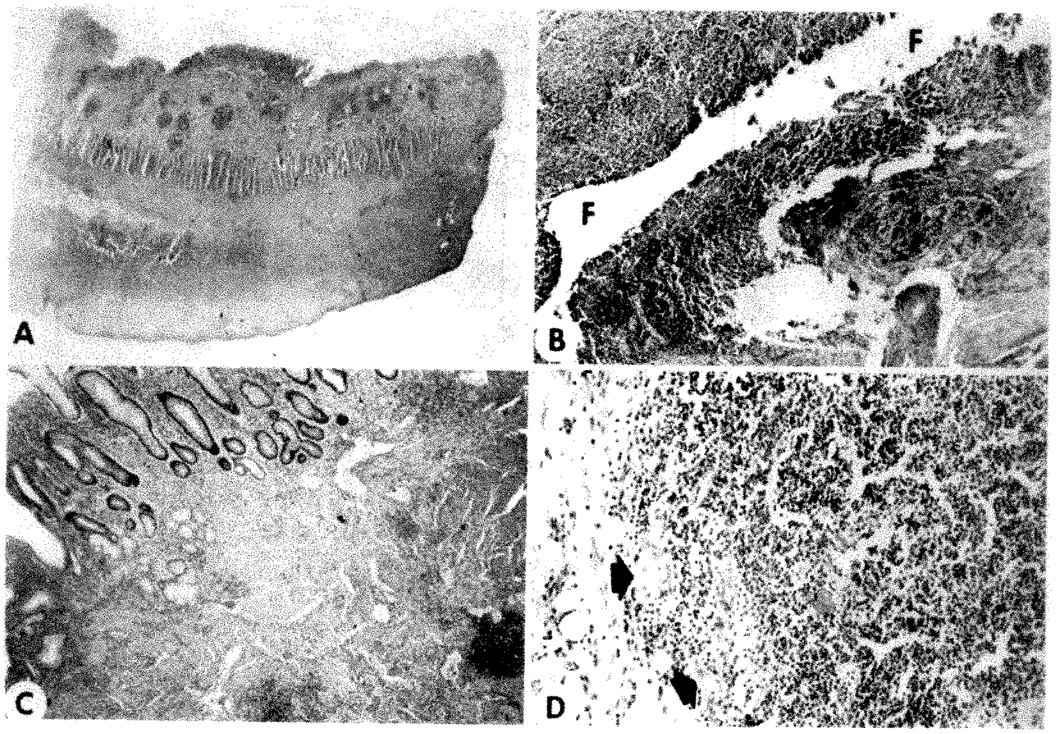

Fig. 1—Microscopic features of the resected ileum.

A. Thickening of the intestinal wall (Hematoxylin and eosin, original magnification x4).

B. Fistulous tract with chronic inflammatory cells and granulation tissue. "F" indicates fistula (Hematoxylin and eosin, original magnification x84).

C. Chronic inflammatory reaction and fibrosis involving mucosa and submucosa (Hematoxylin and eosin, original magnification x48).

D. Granuloma with lymphocytes, plasma cells, histiocytes and foreign body giant cells (arrows) (Hematoxylin and eosin, original magnification x120).

Except for occasional diarrhea, he did quite well after 1964 until April, 1975, when he developed right flank pain, nausea and occasional vomiting. Upper gastrointestinal x-ray series and barium enema were normal. Three weeks later, he was admitted to a local hospital where a retroperitoneal abscess, situated in the right flank, was incised and drained. No nasogastric intubation was done during this hospitalization.

Immediately after this acute illness, he began to have difficulty in swallowing. He denied any "heartburn" or substernal pain. An esophagogram and esophagoscopy revealed superficial ulcers and stricture of the distal esophagus. Biopsy of the esophagus showed only granulation tissue. He was treated with antacids and Maloney bougie dilatation. A transient pneumomediastinitis developed during one esophageal dilatation procedure but Hypaque® swallow study failed to demonstrate perforation or fistula formation from the esophagus. He was unable to eat anthing except blenderized food. His general condition deteriorated, body weight decreased by 9 kg. and alopecia developed. He was transferred to Strong Memorial Hospital on 24 August 1976.

On admission he weighed 56.7 kg. His face was pale, extremities were cold and skin was dry. There was a 3 cm. circular

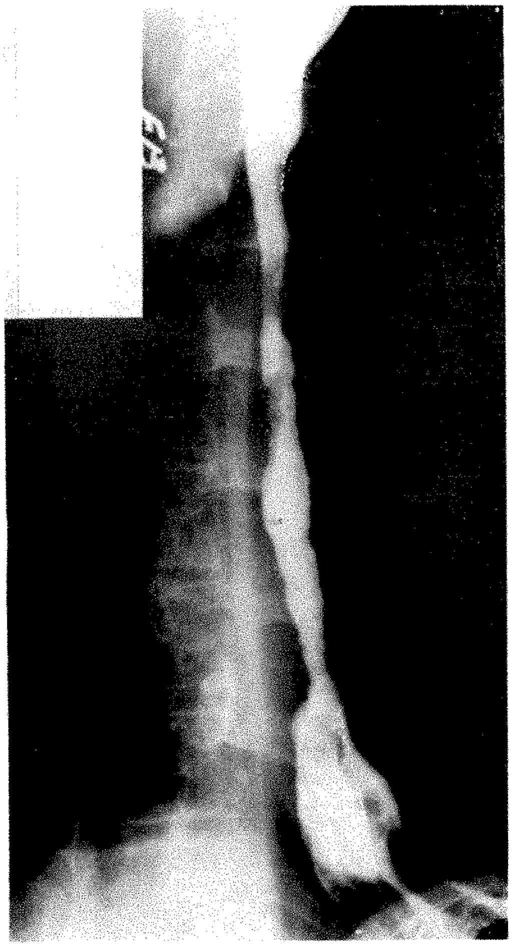

Fig. 2—Preoperative esophagogram shows a long narrow distal esophageal stricture with irregularity of mucosa and a small hiatal hernia.

wound (fistula) with yellowish exudate in his right flank. Serum albumin was 2.5 gm./100 ml. STS and PPD were negative. An esophagogram (Fig. 2) demonstrated a long tubular constriction of the esophagus and a small hiatal hernia. The esophagus was examined with an Olympus GIF-D3 scope. The esophageal lumen was almost obliterated by a stricture 30 cm. from the incisor teeth. A size 20 F Maloney bougie could not be passed through the stricture. The mucosa proximal to the stricture was hyperemic with an irregular surface. Biopsy of the esophagus again showed only granulation tissue. He was given parenteral nutrition with Freamine II and intralipid.

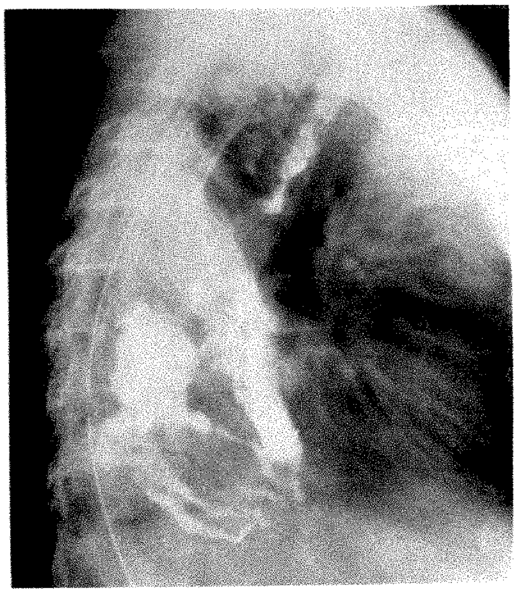

Fig. 3—Postoperative esophagogram shows a gastroesophagostomy and a fistula to the mediastinum.

The esophagus was dilated with a rigid dilator up to 24 French and then by Maloney bougies every other day to size 40 F. He gained 5 kg. of weight in three weeks and was able to eat a soft diet. At this time an Olympus JK duodenoscope could be passed through the strictured area. The stricture was 4 cm. in length and the esophageal mucosa distal to the stricture was normal except for mild hyperemia. The mucosa around the stricture area was hyperemic with an irregular surface, shallow ulcers and pseudomembrane formation. Biopsy of the esophagus proximal and distal to the stricture showed columnar epithelial cells, and biopsy of the strictured area showed granulation tissue with a cluster of atypical mucosal cells suggestive of squamous cell carcinoma. Because of the possibility of carcinoma, part of the esophagus was resected. This was followed by a gastroesophagostomy, pyloroplasty and feed-

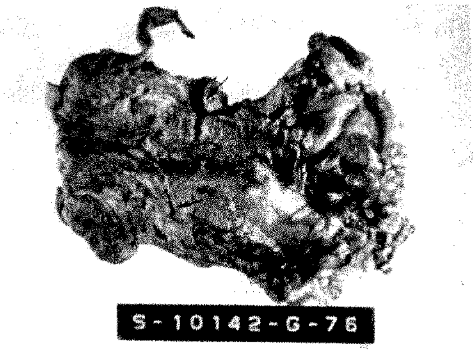

Fig. 4—Gross specimen of the resected esophagus. Right side is cardia of the stomach. Esophageal wall is very thick. Mucosal surface is very irregular. Ulceration, nodulation and fissures (arrows) are seen.

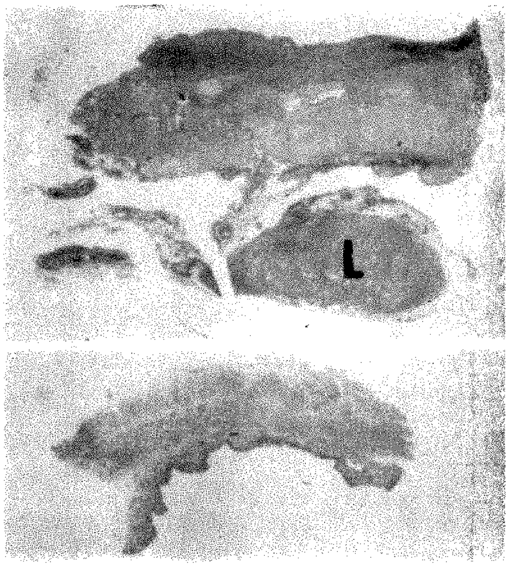

Fig. 5—Comparison of the esophagus of patient (J. L.) (upper) with esophagus of a patient with Barrett's esophagus (J. B.) (lower). Note the marked thickness of the esophageal wall in J. L. (Crohn's esophagus). "L" shows a reactive hyperplastic lymph node along with Crohn's esophagitis.

ing jejunostomy. One week after the operation, pus-like substance was drained from the chest tube. Barium swallow at this time showed an esophageal-mediastinal fistula (Fig. 3).

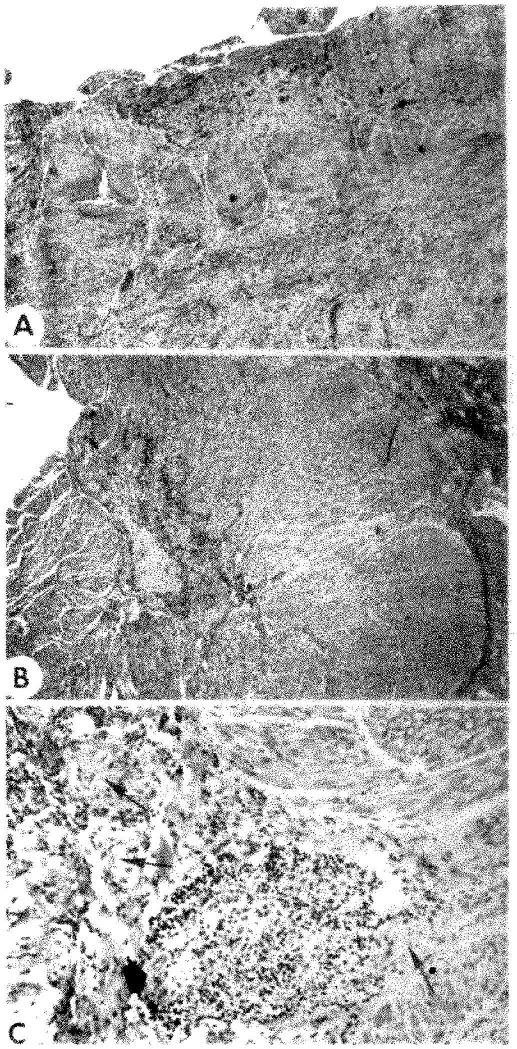

Fig. 6—Microscopic features of the resected esophagus.

A. Chronic transmural inflammation in submucosal and muscular layers. The mucosal layer is denuded (Hematoxylin and eosin, original magnification x30).

B. Hypertrophy of the muscular layer infiltrated with chronic inflammatory cells (Hematoxylin and eosin, original magnification x48).

C. Granuloma in muscle layer with giant cells (wide arrow). Hypertrophic nerves are also noted (thin arrow) (Hematoxylin and eosin, original magnification x120).

The resected esophagus had a very thick wall (Figs. 4 and 5). This is especially evident when the thickness of the

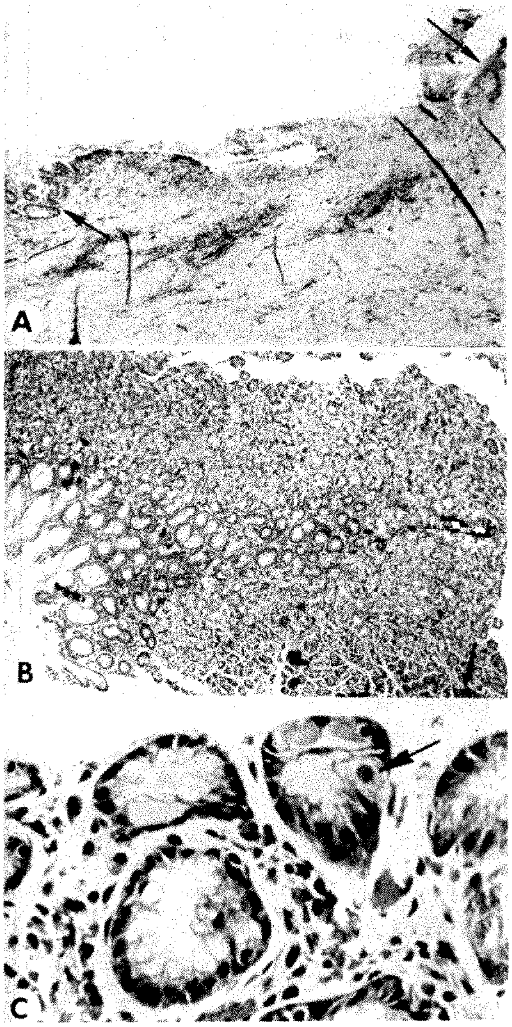

Fig. 7—Features of Barrett's esophagus in patient J. L.

A. Mucosa with squamous epithelium (arrow—right side) and columnar epithelium (arrow—left side) are demonstrated at the same level of the proximal resected esophagus (Hematoxylin and eosin, original magnification x30).

B. Barrett's esophagus with gastric fundal type mucosa and some intestinal villous projection (Hematoxylin and eosin, original magnification x48).

C. Oxyntic cells (arrow) in the gastric gland of the fundal type of Barrett's esophagus (Hematoxylin and eosin, original magnification x500).

esophagus is compared with the thickness of that of a patient with reflux esophagitis and Barrett's esophagus using a macro lens (Fig. 5). The mucosal surface of the esophagus was very irregular with a cobblestone appearance containing ulcerations and fissures (Fig. 4). Microscopically, there was transmural chronic inflammation (Figs. 6A and 6B) and hypertrophy of the muscular layer (Fig. 6B). Granulomatous and neuromatous hypertrophic lesions were found along with the marked inflammatory process (Fig. 6C). The Barrett's mucosa was also found in the resected esophagus (Fig. 7). In the same biopsy specimen, stratified squamous epithelium was seen on one end and columnar epithelium on the other, with mucosal ulceration in between (Fig. 7A). Distal to the stricture, gastric fundal type mucosa and metaplastic intestinal mucosa were observed (Fig. 7B). Oxyntic cells were noted in the fundal type mucosa (Fig. 7C).

The patient developed two episodes of septicemia during his hospital stay which were controlled by antibiotics. The esophagomediastinal-cutaneous fistula finally closed after three months on elemental diet feedings through a jejunostomy tube. The patient feels well now and can eat a soft diet by mouth. The fistula in his abdomen, however, is not completely healed and drains occasionally.

COMMENT

This patient had a classical clinical picture of Crohn's disease manifested by diarrhea, intestinal obstruction, retroperitoneal abscess, enteric fistula, anal fistula and sacroileitis. The resected terminal ileum demonstrated transmural inflammation and epithelioid giant cell granuloma. Later in the course, he developed an esophageal stricture. The resected esophagus showed transmural inflammation, muscular hypertrophy, neuromatous lesions with hypertrophied nerves and areas of granuloma formation. These features are very suggestive of Crohn's disease of the esophagus.

Other etiological factors that might cause esophageal stricture in this patient were considered. One possibility was reflux esophagitis reflected by the presence of Barrett's esophageal mucosa. Neither his clinical symptoms nor the histologic findings of the resected esophagus, however, suggested reflux esophagitis. In reflux esophagitis, lesions are mainly in the mucosa and the submucosa and the greatest amount of cellular infiltration is found closer to the epithelium.[18] Also, muscle hypertrophy, neuromatous and granulomatous changes have not been reported in reflux esophagitis.[18]

Trauma can cause foreign body granuloma. Our patient had a pneumomediastinum during an esophageal dilatation procedure. It is unlikely, however, that the long-segment, transmural, granulomatous inflammation was caused by a small traumatic perforation. Fungal diseases, tuberculosis and syphilis may present granulomatous lesions. There was no evidence of these infections in this patient.

It is extremely rare to see Crohn's disease involving the esophagus. In 1969, Dyer, et al[12] reported two patients with Crohn's disease of the esophagus and reviewed the 12 previously reported cases of Crohn's disease of the esophagus. These authors were unable to find any patient with Crohn's disease of the esophagus in 2,520 patients with Crohn's disease of the bowel reported in the literature. Marshak,[19] likewise, did not find any instance of Crohn's disease of the esophagus in his 8,000 cases of regional enteritis and 4,000 cases of granulomatous colitis.

Thus far, only 15 cases of Crohn's disease of the esophagus have been reported in the English literature. On endoscopic biopsy, five (Table I, Cases 1, 2, 4, 5, 11 and 15) of these had insufficient esophageal mucosa and only one (Case 15) showed giant cell granuloma in the submucosa. Transmural change was not displayed. The diagnosis was presumptive in these cases and was found in the presence of an unusual esophageal stricture[7] or the existence of an esophageal lesion in patients who also had manifestations of Crohn's disease.[8, 12, 16] Nine (Table I, Cases 3, 6, 7, 8, 9, 10, 12, 13 and 14) patients were diagnosed from examination of resected specimens obtained at surgery or at autopsy. Four (Table I, Cases 7, 9, 10, and 13) of these patients showed only thickening of the esophageal wall with transmural fibrosis and chronic inflammation; two (Table I, Cases 3 and 8) were described as similar to Crohn's disease; and three (Table I, Cases 6, 12 and 14) had granulomas in the pathology specimen. No giant cells were seen in the two patients (Table I, Cases 6 and 12) in whom histological material was available. Although the presence of giant cells is not a *sine qua non* for the diagnosis of Crohn's disease, their presence and their absence weighs against excluding favor this diagnosis. Therefore, one may argue the diagnosis of Crohn's disease of the esophagus. On the other hand, however, two patients reported by Dyer[12] and one reported by Cynn[15] had Crohn's disease of the small intestine. They, however, did not have classical pathological features of granuloma formation in the esophageal specimen.

Crohn's disease is commonly seen in the small and large bowel which have columnar epithelium. Therefore, it is possible that Crohn's disease has a predilection for columnar epithelium. If this is true, then the patients with Barrett's esophagus may have Crohn's esophagitis because of its columnar epithelium. Our case is the only

TABLE I

Review of Cases Reported as Crohn's Esophagitis in the Literature

Patient	Reference	Diagnostic evidence	Histology of esophagus	Other gastrointestinal tract involvement
1. C. M.	Franklin[7]	High esophageal stricture.	Granulation tissue.[*][‡]	No
2. M. E. M.	Franklin[7]	Long esophageal stricture.	Granulation tissue.[*][‡]	No
3. L. C.	Franklin[7]	High esophageal stricture with surgically resected esophagus.	Presumptive Crohn's disease.[†][‡]	No
4. –	Heffernon[8]	Polypoid mass in lower esophagus with remittant chronic inflammation of stomach and small intestine.	Edema and chronic inflammatory cells infiltration in stoma.[*][‡]	Stomach, duodenum and upper jejunum.
5. –	Gelfand[9]	Dysphagia, histopathology of the rectal biopsy, cobblestone lesion in cecum by barium enema.	Mild focal submucosal esophagitis.[*][‡]	Anal fissure, rectal ulcer.
6. A. V.	Turina[10]	Stenosis of lower esophagus, surgical and pathological findings.	Thickening of the esophageal wall with granulomatous lesion,[†] no giant cell.	No
7. J. K.	Madden[11]	Long esophageal stricture, surgical and pathological findings.	Extensive submucosal and transmural fibrosis.[†]	No
8. R. C.	Madden[11]	Tubular stenosis of lower esophagus, surgical and pathological findings.	Presumptive regional esophagitis.[†][‡]	No

TABLE I (*continued*)

REVIEW OF CASES REPORTED AS CROHN'S ESOPHAGITIS IN THE LITERATURE

Patient	Reference	Diagnostic evidence	Histology of esophagus	Other gastrointestinal tract involvement
9. M. E.	Madden[11]	Long esophageal stricture, surgical and pathological findings.	Extensive fibrosis and focal inflammatory infiltrates in the submucosa and muscle layers.†	No
10. J. W.	Dyer[12]	Narrowing of lower esophagus associated with Crohn's ileitis.	Edema and dense fibrosis in submucosa and muscle layer, focal collection of plasma cells and lymphocytes, hypertrophy of nerve fibers.†	Mouth ulcerations, Crohn's disease in lower jejunum and ileum.
11. L. B.	Dyer[12]	Dysphagia and irregularity of lower esophagus in esophagram associated with regional ileitis.	Edema and nonspecific inflammatory changes in submucosa.*‡	Regional ileitis Recurrent mouth ulceration.
12. M. B.	Livolsi[14]	Lower esophageal stricture, surgical and pathological findings.	Submucosal edema, intramural fibrosis and muscular hypertrophy, granulomatous lesion, no giant cells.†	No
13. E. B.	Cynn[15]	Esophageal fistula, autopsy finding.	Transmural chronic inflammation without granuloma.‡	Ileocolitis.
14. A. A.	Cynn[15]	Esophageal fistula, surgical and pathological findings.	Transmural chronic inflammation with noncaseating granuloma.†‡	Rectal fistula.
15. –	Miller[16]	Mid esophageal stricture diffuse.	Granulomatous inflammation.*	Diffuse granulomatous colitis, oral ulcer, rectal abscess and fistula.

* Tissues obtained from peroral esophageal biopsy.
† Tissues obtained from surgical resection.
‡ No histology illustrated.

example of which we are aware showing these two diseases simultaneously.

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Cardiovascular Responses to Upper Gastrointestinal Endoscopy

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Continuous Holter monitoring and serial blood pressure recordings were obtained during upper gastrointestinal endoscopy on 51 unselected patients, 18 with cardiovascular disease. Sedation with intravenous diazepam produced a small but significant fall ($P < .001$) in blood pressure, heart rate and rate-pressure product. During endoscopy, the blood pressure rose only to base line levels but the heart rate and rate-pressure product went significantly higher ($P < .001$). Nine subjects (five with pre-existing cardiovascular disease, four normal) exhibited electrocardiographic changes, including supraventricular arrhythmias, ventricular ectopy and significant ST segment depression. None of the patients had bradycardia or significant vagal symptomatology. The difference in incidence of abnormalities between the normal patients (4/33) and those with cardiovascular disease (5/18) was not statistically significant ($P = 0.3$). Endoscopy can be safely performed even in patients with cardiovascular disease but attention to the reduction of cardiac stress would further increase its safety.

Upper gastrointestinal endoscopy has been shown to be a remarkably benign procedure, with a very low incidence of morbidity and mortality.[1, 2] Prospective studies of cardiac responses during fiberoptic upper gastrointestinal endoscopy have reported varying incidences of ischemic ST segment change, atrial or ventricular ectopy and numerous arrhythmias, all of which appear more frequently in patients with underlying cardiovascular disease.[3-6] Fortunately, most such disturbances remitted spontaneously without additional complications. Although such evidence strongly suggests that endoscopy can be safely performed in cardiac patients, further confirmation is clearly warranted. The optimum approach to such patients, in terms of selection, pre-medication and monitoring, still remains to be determined.

In the present study, systematic clinical observation and two-channel Holter monitoring were used to evaluate prospectively the cardiac responses to upper gastrointestinal endoscopy in 51 unselected subjects, 18 of whom had cardiovascular disease.

METHODS

Fifty-one unselected patients, 37 males and 14 females, undergoing upper gastrointestinal endoscopy were studied. They ranged in age from 18-88 years, with a mean of 47 years. Patients were chosen because of demonstrated need for endoscopy; none were excluded because of underlying heart disease. A careful cardiac history and

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TABLE I

Endoscopic Diagnoses in Gastrointestinal Examinations

Diagnosis	Number of patients	Number of lesions with acute bleeding
Normal	17	
Duodenal ulcer	18	5
Esophagitis	7	
Gastritis	5	1
Gastric carcinoma	1	
Esophageal carcinoma	1	
Gastric bezoar	1	
Incomplete examination	1	
Total	51	6

TABLE II

Cardiac Diagnoses in 18 Patients*

	Number
Definite coronary artery disease	5
Abnormal resting electrocardiogram (only)	2
Anterolateral T wave inversion	
Unifocal VPB's	1
Conduction abnormality	
Left anterior hemiblock	2
Right bundle branch block	1
Valvular heart disease	
Mitral stenosis/regurgitation	1
Mitral valve prolapse	1
Hypertension	7
Hypertensive heart disease	1

* Diagnoses are not mutually exclusive.

examination by a cardiologist were performed immediately prior to the procedure. An electrocardiogram, chest x-ray, serum electrolytes, BUN, blood glucose, hemoglobin, and digoxin level (if appropriate) were obtained on all patients. Except for the routine fasting period prior to endoscopy, no maintenance medications were discontinued. No patient was treated with agents such as propranolol, which affect the rate-pressure product. Intravascular volume correction was initiated in all acutely hemorrhagic subjects before endoscopy.

Prior to endoscopy, each patient was outfitted with a portable Holter monitor (Avionics #445 Electrocardiocorder) allowing continuous recording of modified leads V1 and V5. Each patient was monitored for at least ten minutes before and after endoscopy, as well as throughout the procedure. Recordings were analyzed on an Avionics #660A Electrocardioscanner with arrhythmia and ST level computers. This system provides continuous analyses of both heart rate and ST segment displacement in lead V5. The arrhythmia computer was set to provide 15-second real-time recordings of any ectopic beats or arrhythmias. All tracings were directly reviewed for positive identification of the reported abnormalities.

Subjects were pre-medicated with sufficient intravenous diazepam (1-20 mg.) to produce adequate relaxation, as evidenced by slurred speech. All procedures were performed by an experienced endoscopist with patients in the left lateral decubitus position, using an ACMI 7089-P panendoscope. Concomitant oropharyngeal suctioning was performed to minimize aspiration of secretions and gagging.

Blood pressure was measured by sphygmomanometry before and after premedication and at five-minute intervals throughout endoscopy or immediately prior to instrument withdrawal in shorter procedures. The rate-pressure product was

TABLE III

HEMODYNAMIC RESPONSES DURING ENDOSCOPY

	Base line	With sedation	During procedure
Blood pressure	132 ± 3* 84 ± 2	124 ± 3 78 ± 2 (P < .001)	133 ± 3 83 ± 2 (P > .05)
Heart rate	78 ± 2	71 ± 2 (P < .001)	105 ± 3 (P < .001)
Rate-pressure product**	98 ± 3	84 ± 3 (P < .001)	130 ± 4 (P < .001)

* All values represent mean ± SEM. P values are for comparison to base line data by paired 2-tail Student's "t" test.

** Calculated as systolic BP × HR/100.

calculated as the product of the systolic blood pressure and heart rate divided by 100.[7] Statistical significance was calculated by Student's "t" test.

The nontherapeutic research nature of the Holter monitoring was fully explained to each patient and informed consent was obtained prior to the study. The protocol was approved by the Walson Army Hospital Committee on Human Studies.

RESULTS

Total panendoscopy was accomplished in 47 patients. In two, the duodenum was not visualized because of pyloric stenosis; in another, only the esophagus was examined because of an obstructing carcinoma. In a fourth subject, the instrument could not be passed beyond the cricopharyngeus muscle. The average duration of the procedure was nine minutes, ranging from one to 26 minutes. The diagnoses determined at endoscopy are presented in Table I.

Clinical evaluation revealed various cardiovascular abnormalities in 18 patients (Table II). Coronary artery disease was diagnosed only if a patient had either a prior myocardial infarction, documented by electrocardiogram or clinical history, or a chest pain syndrome typical for angina with associated electrocardiographic ischemic changes documented during exercise testing or prior hospitalization. Chest pain syndrome or nonspecific electrocardiographic changes alone were considered insufficient to diagnose coronary artery disease.

HEMODYNAMIC RESPONSES

Sedation with diazepam produced a small but significant (P < .001) fall in heart rate, blood pressure and rate-pressure product. During endoscopy, the blood pressure rose only to the presedation level. There was, however, a marked rise in mean heart rate, resulting in a significant increase in the rate-pressure product, compared to either base line (P < .001) or postsedative (P < .001) levels (Table III).

ELECTROCARDIOGRAPHIC ABNORMALITIES

Nine patients exhibited electrocardiographic abnormalities during endoscopy (Table IV). Sinus tachycardia, infrequent (< 10% of total beats) atrial or ventricular unifocal ectopy and isolated T wave changes were disregarded. Two patients had brief runs of paroxysmal atrial tachy-

TABLE IV

ELECTROCARDIOGRAPHIC ABNORMALITIES DURING ENDOSCOPY

Patient	Underlying cardiovascular disease	Electrocardiographic abnormalities	Change in rate-pressure product
1	None	Brief atrial tachycardia	+ 39%
3	None	Frequent unifocal VPB's	+ 19%
28	None	I mm. horizontal ST depression	+ 106%
40	None	2 mm. upsloping ST depression	+ 11%
34	Occasional VPB on resting electrocardiogram	Marked increase frequency VPB's	− 16%
41	Acute myocardial infarction	1 mm. upsloping ST depression	+ 15%
42	Hypertensive heart disease	Brief atrial tachycardia 1.5 mm. horizontal ST depression	+ 8%
49	Hypertension	2 mm. upsloping ST depression	+ 56%
51	Hypertension	1 mm. upsloping ST depression	+ 80%
		Total mean	+ 35%

cardia which remitted spontaneously without evident hemodynamic compromise. Two patients exhibited marked unifocal ventricular ectopy (> 10% of total beats); couplets, multifocal beats, or ventricular tachycardia were not observed. Two patients had horizontal ST segment depression and three patients had upsloping ST segment depression of at least one mm. 0.08 seconds after the j point. None of the patients experienced chest pain during or after endoscopy. The incidence of cardiac abnormalities tended to be higher in the patients with cardiovascular disease (5/18) than in those apparently normal (4/33) but the difference was not statistically significant ($P = 0.3$). There was no relationship between the occurrence of cardiac abnormalities and patient age or procedure duration. The mean increase in rate-pressure product for patients with electrocardiographic changes (+ 35%) did not differ significantly from the mean increase in the entire study population (+ 33%).

None of the patients developed bradycardia or vagal symptomatology during the procedure. The patient with mitral valve prolapse had frequent atrial premature beats at rest which disappeared during endoscopy, presumably suppressed by the resultant sinus tachycardia. One patient was studied because of recurrent hemorrhage two days after an acute subendocardial myocardial infarction. Although upsloping ST segment depression developed during endoscopy, there was no chest pain, ectopy, arrhythmia, or evidence of subsequent extension.

COMMENT

The major prospective studies of cardiac response to fiberoptic upper gastrointestinal endoscopy, including the present one, indicate that ischemic ST segment changes, ventricular ectopy and arrhythmias are frequent, especially in patients with underlying cardiovascular disease.[3-6] These are summarized in Table V.

TABLE V

Prospective Evaluations of Cardiac Responses During Fiberoptic Upper Gastrointestinal Endoscopy

Authors	Patients	Number with cardiovascular disease	Premedication	Method of monitoring	Number with electrocardiographic changes			
					ST Segment			
					changes	VPB's	Arrhythmia	Bradycardia
Sturges, et al[3]	60	16	Diazepam Meperidine Pharyngeal anesthesia	Continous standard EKG	0	1	0	1
Pyöröla, et al[4]	101	39	Atropine Phenobarbital Pharyngeal anesthesia	Continuous standard EKG	21	22	0	0
Fujita, et al[5]	86	59	Balethamate Pharyngeal anesthesia	Intermittent standard EKG	27	9	5	0
Van Durme, et al[6]	52	16	Pharyngeal anesthesia	Holter monitor	8	13	0	0
Present report	51	18	Diazepam	Holter monitor	5	2	2	0

There is considerable literature documenting the various vagovagal reflexes which may result from pharyngeal manipulations or distention of hollow viscera.[8-13] Their potential for cardiovascular morbidity has made them a matter of concern to endoscopists, leading some to prophylactic premedication with atropine. It is significant that in our report and in the other prospective studies of fiberoptic upper gastrointestinal endoscopy where atropine was not used, only a single case of otherwise benign bradycardia was noted in 149 patients.[3, 5, 6] We conclude that there is currently no prospective evidence to implicate vagovagal reflexes in the cardiovascular abnormalities associated with endoscopy.

The fact that ischemic ST segment changes and ectopy occurred in nine of our 51 patients, a frequency consistent with prior reports[5, 6] and that idiosyncratic vagal reactions are unusual, suggests that cardiac stress is primarily responsible. We have used the rate-pressure product to assess the increased cardiac minute-work load during endoscopy. Despite its simplicity, it has been shown to predict reliably the work load at which individuals with coronary artery disease develop angina.[7] Our findings of a mean increase in rate-pressure product of 33% indicate that endoscopy represents a mild but significant form of cardiac stress. Sturges, et al,[3] however, found no over all increase in rate-pressure product in their patients but this difference may relate to consistently heavier sedation and severe hemorrhagic hypotension in several patients. Pyöröla, et al[4] measured only changes in heart rate, certainly the major determinant of rate-pressure product increase and reported a mean increase during endoscopy similar to our findings.

Routine cardiac stress testing is associated with an increase in rate-pressure product of 200-300% and a mortality of 0.010%.[14] Endoscopy, which produces a considerably smaller increase in rate-pressure product, has been associated with a proportionately lower cardiac mortality (0.002%) in large retrospective surveys.[1-2] The apparent dichotomy between the relative frequency of electrocardiographic abnormalities reported in prospective studies and the low cardiac mortality in surveys probably results from the low level and short duration of cardiac stress during endoscopy.

As endoscopic procedures become even more widespread and more cardiac patients are studied, the cardiac mortality will inevitably rise. No prospective study of cardiac patients could be large enough to provide the endoscopist with optimum methods of management based on mortality figures. Clearly the management of such patients must be based upon general principles which minimize cardiac stress. Adequate sedation, the continuation of maintenance propranolol, and the avoidance of prophylactic atropine may all be useful in preventing inordinate increases in the rate-pressure product. In the patient with severe angina, a preliminary treadmill exercise test may be useful in predicting the likelihood of an ischemic response during endoscopy. The subject who develops angina or ischemic electrocardiographic changes at a low rate-pressure product may benefit from cardiac monitoring throughout the procedure. The acute prophylactic administration of nitrates, propranolol, or xylocaine to such patients may well be beneficial and represents an area for future investigation. The production of arrhythmias by cardiac stress is less frequent and less predictable than the production of ischemic electrocardiographic responses. Patients with severe valvular or coronary artery disease or marginally compensated congestive heart failure may tolerate prolonged arrhythmias poorly. Such patients should probably be monitored during endoscopy and may benefit from antiarrhythmic prophylaxis.

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Communication from Abroad

Adrenergic Influences on the Gallbladder Emptying

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Dihydroergotamine (DHE) (or phentolamine), an alpha-adrenergic blocking agent, induced important changes on the CCK-stimulated gallbladder emptying of 70 volunteer subjects. Two cholecystograms were performed with 10-day intervals in each subject. The first cholecystogram showed gallbladder emptying provoked by a test meal (35 subjects or by 0.5 U. CCK Kg. injected intravenously (35 subjects). During the second cholecystogram 1 mg. of DHE was injected intramuscularly 45 minutes before the cholecystokinetic stimulus. The drug counteracted the gallbladder emptying induced by both endogenous and exogenous CCK. The effect was more pronounced when DHE was administered prior to the test meal stimulus than before CCK administration. This difference could be explained by a delayed gastric emptying induced by the alpha-adrenergic blockade. Our results suggest that the lack of gallbladder emptying could be due to the relaxation of this organ, in addition to a duodenal spasticity induced by DHE (or phentolamine).

INTRODUCTION

Poor emptying of the gallbladder and biliary stasis have been considered important factors in the generation of many gastrointestinal symptoms.

Hormonal control of the extrahepatic biliary system appears to be a responsibility of cholecystokinin (CCK), which is released by the proximal small bowel.[1] CCK contracts the gallbladder[2] and relaxes the sphincter of Oddi.[3]

Also, in the gallbladder and the sphincter there are contraction-mediating cholinoreceptors and contraction-mediating alphareceptors. Relaxation-mediating beta-receptors are also found in the gallbladder and in the sphincter.[4] Despite, however, the extensive literature, no consensus exists concerning the relationship between hormonal and neural controls. Moreover, neural influences have been considered of minor importance[1, 5] because CCK acts directly on specific receptors and because no interferences by anticholinergic, antiadrenergic and depolarizing agents or tetrodotoxin, were performed.[6, 7] Because, however, important changes of the distal colon motility were induced by dihydroergotamine (DHE) and phentolamine in patients affected by the "irritable bowel syndrome",[8, 9] it seemed

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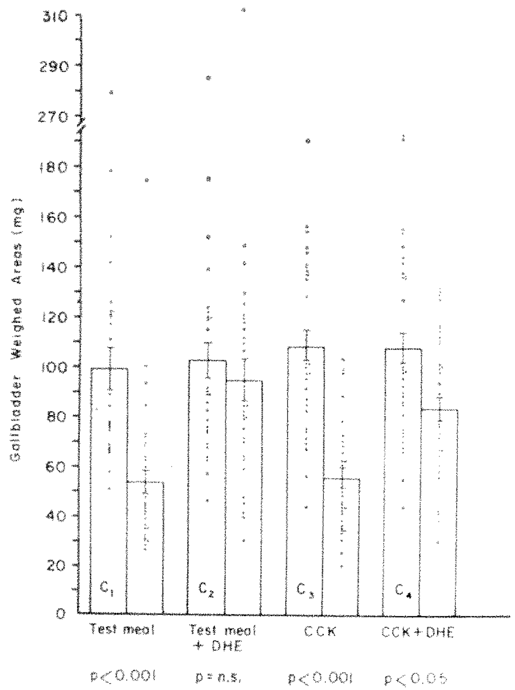


Fig. 1—Effect of dihydroergotamine (1 mg. injected I.M.) on induced gallbladder emptying. C_1, C_2, C_3, and C_4 = control gallbladder integrated areas. Right side attached bars = Poststimulus gallbladder integrated areas. Vertical lines = SEM.

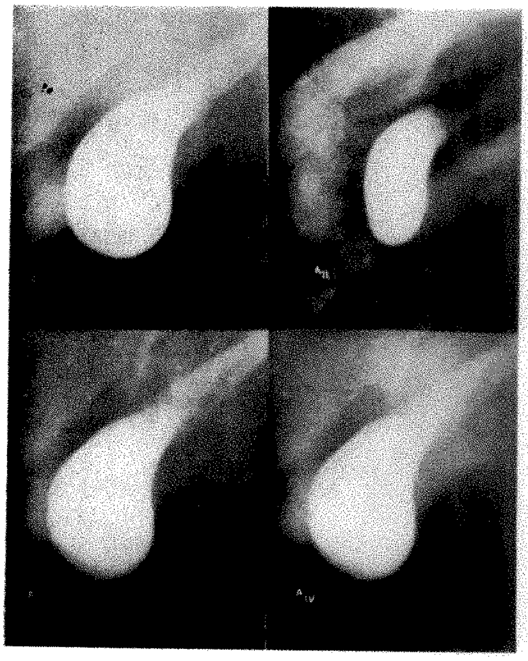


Fig. 2—Gallbladder images from a subject in control conditions before (A_I) and 30 minutes after the test meal (A_{II}). No gallbladder emptying was observed (A_{III} and A_{IV}) on the same subject in a second cholecystography ten days after the first, when dihydroergotamine (1 mg. I.M.) had been injected 45 minutes before the test meal.

of interest to investigate the effect of that drug on the gallbladder emptying of subjects stimulated by endogenous or exogenous CCK.

PATIENTS AND METHODS

Subjects:—Our protocol included 70 volunteer subjects, 36 female and 34 male. Ages ranged between 18 and 54 years, mean 36.7 years. All the subjects were admitted to a gastroenterological clinic (Instituto de Vías Digestivas de Caracas) for a thorough investigation of gastrointestinal, metabolic, infective or drug-induced diseases. The exclusion of organic diseases was a prerequisite for including subjects in our casuistic.

We divided our patients in two groups of 35 subjects each: the first one, 19 female and 16 male; the second one, 17 female and 18 male.

Radiological procedures:—An oral cholecystogram was performed on all subjects, employing a double dose of iopanoic acid (Telepaque®). In the first group, the gallbladder emptying was obtained by means of a test meal (250 ml. milk + 2 egg yolks + 2 teaspoonfuls butter). In the second group, 0.5 U. Kg. of CCK (GIH) I.V., slowly injected, was employed instead of the test meal. It was found that this dose provoked a cholecystokinetic effect of the same order as our routine test meal. The gallbladder emptying was investigated one half, two and 24 hours after the test meal ingestion or the CCK injection. A second cholecystogram was done on the

70 volunteer subjects 10 days after the first one. During this interval, subjects did not take any drug or change their alimentary habits. No intercurrent diseases were observed during the interval. For this second occasion, 1 mg. of DHE was injected I.M. 45 minutes before the test meal or the CCK administration. In six subjects, phentolamine (Regitine, Ciba) 5 mg. I.M. was injected instead of DHE. An additional x-ray film was made immediately before the test-meal or the CCK injection which showed that DHE (or phentolamine) did not produce any change of the control gallbladder image. It was shown too, that each subject had identical gallbladder images in both cholecystographies, before the cholecystokinetic stimulus. The roentgen technic was identical for each patient.

Measurements of gallbladder emptying:—For the quantitative measurement of gallbladder emptying, the x-ray images were traced on millimetered paper and subsequently weighed. Before the weighing of the gallbladder circumscribed areas, the weights were verified of the two 100 cm.^{2} of papers in which they were respectively included; the difference between the weighings was always less than 2 mg. The magnitude of emptying was expressed in percentage.

In addition to the changes of size, the changes of shape and position of the gallbladder were registered. The visualization of biliary ducts was also registered. Finally, the symptoms provoked by the dye ingestion, the cholecystokinetic stimulus and the DHE injection, were also registered.

Statistical analysis:—We employed the Student "t" test. We found the standard error of the difference between two means and tested the size of the difference by this standard error. We used the standard deviation of each sample, computed separately, to calculate the standard error of the difference between the means.

In calculating "t" on the paired observations, we worked with the difference, "d", between the members of each pair. For this purpose, we found the mean of the difference between the observations and then the standard error of the means.

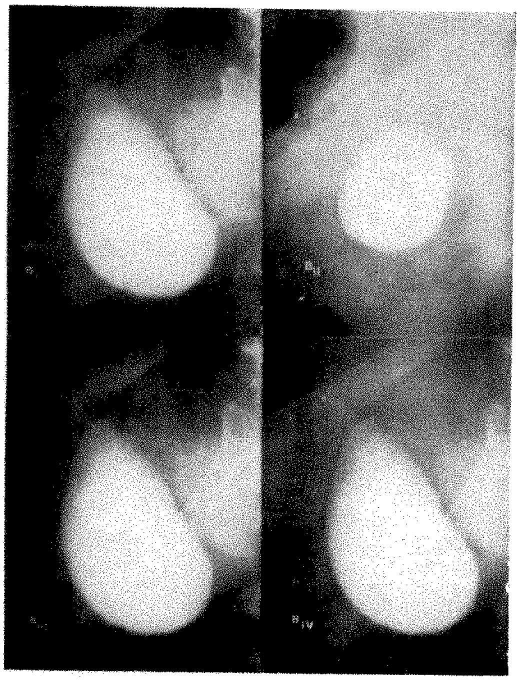
RESULTS

The absolute values are presented in Figure 1. The same values are expressed in percentages in the text.

Test meal:—In this group, gallbladder emptying was produced in all cases. Range of emptying = 34.4-64.3%, mean ± SE = 48.62% ± 2.3. There were no differences between the gallbladder images obtained at 30 and 60 minutes. In five of the 35 subjects, the gallbladder was still visualized 24 hours after the ingestion of the test meal.

CCK:—Range of emptying = 32.8-57.4%; mean ± SE = 44.53% ± 0.98. There were no differences between the 30- and 60-minute images. The gallbladder was still visible in the 24-hour film in seven of 35 cases. The difference between the mean percentages of emptying (CCK vs. test meal) was not significant. Neither the test meal nor the CCK injection provoked intolerance symptoms in the studied patients.

Test meal + DHE (or phentolamine):—Range of emptying = −16.6-59.5%; mean ± SE = 8.08% ± 2.7. Only in one subject did we find a normal emptying. In 17 patients, the emptying was $< 27\%$, in five subjects the emptying was $< 5\%$ and in 12 cases the gallbladder areas increased. The gallbladder emptyings in the 3-phentolamine injected patients were: 15, 12.1 and 6.5%. There were no differences between films obtained at 30 and 60 minutes. In 22 of the 35 patients the gall-



ig. 3—Gallbladder images before (B_I) and 30 minutes after (B_{II}) the I.V. injection of 0.5 U.Kg. of CCK. No gallbladder emptying was observed (B_{III} and B_{IV}) in a second cholecystography on the same subject, ten days after the first. On this occasion, dihydroergotamine (1 mg. I.M.) was injected 45 minutes before CCK.

ladder was still visible in the 24-hour film. his value was significantly greater than he five of 35 cases registered without DHE njection, $P < 0.001$. DHE injection before he test meal produced a mean percentage f gallbladder emptying significantly lower han that produced by the test meal alone, < 0.001. In 13 of 35 DHE injected subects, the test meal produced intolerance ymptoms (headache, nausea, vomiting, ostprandial distress, dizziness, etc.). Figre 2, shows a typical case of DHE-induced mpairment of gallbladder emptying stimlated by test meal.

CCK + DHE (or phentolamine):—he range of emptying = − 18.2-56.6%; ean ± SE = 22.1% ± 2.97. In only two ubjects did we find a gallbladder emptying > 40%. A deceased gallbladder emptying was registered in 29 cases, in six of which the emptying was lower than 5%. An increased gallbladder area was obtained in four patients. The gallbladder emptyings in the 3-phentolamine injected patients were: 13, 8.4 and 5.3%. No differences between films obtained at 30 and 60 minutes were observed. In 18 of the 35 cases of this group, the gallbladder was still visible in the film taken 24 hours after the CCK injection. This value was significantly greater than the seven cases registered in the control series, $P < 0.001$. Figure 3 shows a typical case of DHE-induced impairment of gallbladder emptying by CCK stimulation.

From the comparison of mean emptying, between control (CCK) and (DHE + CCK) series, a highly significant difference was obtained, $P < 0.001$. Only in two cases did CCK produce intolerance symptoms among the 35 patients previously injected with DHE or phentolamine.

It is obvious that the reduction of the mean emptying induced by DHE (or phentolamine) was greater in the test meal than in the CCK group. In the former, the mean emptying decreased from 48.6% ± 2.3 to 8.08% ± 2.7, whereas in the latter group the mean emptying decreased from 44.5% ± 0.98 to 22.1% ± 2.97. When both DHE decreases were compared, the resulting difference was significant, $P < 0.001$. This showed that a greater impairment of the gallbladder emptying was provoked by the drug in the test meal than in the CCK group.

COMMENT

Dihydroergotamine (or phentolamine), an alpha-adrenergic blocking agent, annulled or reduced the gallbladder emptying induced by endogenously released or exogenously administered CCK. This effect of the hormone was obtained in humans in spite of the proven fact that its action was directly exerted on the biliary tract involving no mediation by nerve.[10]

In order to explain the effect of DHE, some mechanisms could be invoked: 1. A blockade of the gallbladder contraction-mediating alpha-adrenoreceptors. This hypothesis would be discarded because there are CCK-receptors which remain free after that blockade.[6] 2. Contraction of the sphincter of Oddi. Against this possibility would be the following facts: a. The alpha-adrenorecptor blockade would favor the relaxing action of the beta-adrenoreceptors. b. DHE did not increase the bromosulfalein retention test, routinely performed along with cholecystography in all the subjects (unpublished results). c. In no case did DHE provoke superior abdominal pain. On the contrary, this drug relieved biliary tract pain 15-20 minutes after I.M. injection (unpublished results). 3. A beta-adrenergic gallbladder relaxation as a result of alpha-adrenergic blockade. Actually, DHE could induce this effect, both centrally and peripherally. With respect to the latter, the presynaptic blockade of the alpha-receptors would increase the release of norepinephrine at the synaptic level,[11, 12] whereas the postsynaptic alpha-blockade would allow only the beta-adrenoreceptors to remain free. In support of his hypothesis would be 2 facts: a. It has been shown that the beta-adrenergic counteracts the CCK-effects both in the gallbladder and in the sphincter of cats. b. Ten milligrams of oral propranolol made the DHE-induced intolerance symptoms disappear. 4. An impairment of biliary drainage due to an increase of the duodenal tone. Actually, we observed radiologically that DHE induced a duodenal spasticity in addition to a gastric hypotony (unpublished results). These findings agree with those of Cook,[13] who showed a slowed gastric emptying of test meals after the intravenous administration of alpha-adrenergic blocking agents. This delayed gastric motility could explain the greater impairment of gallbladder emptying provoked by DHE after the test meal stimulus than after CCK injection. Further, it could explain also the postprandial symptoms observed in 13 of the 35 subjects receiving DHE before the test meals.

The accentuated duodenal spasticity produced by DHE would be due to cholinergic hyperactivity induced by the alpha-adrenergic blockade. The proven high degree of sympathetic activity in the duodenum,[14] in addition to the known antagonism between cholinergic and alpha-adrenergic systems observed at plexa level,[15, 16] fits well with that phenomenon. This fact would be in agreement with the increase of intestinal tone induced by the drug at the distal colon level,[8, 9] in which a high degree of sympathetic activity is also present.[17-19]

Duodenal spasticity in humans is a frequent finding on x-ray, which can occur spontaneously without the administration of drugs. On the other hand, it is known that morphine[20] and diphenoxylate[21] stimulate duodenal motility. These drugs act through the release of 5-HT existing in the myenteric plexus of Auerbach[22] which, besides stimulating the neural elements,[16, 20, 23, 24] acts directly on the smooth muscle fiber.[16, 20, 24-27] Following from the above, it is logical to assume that DHE, on blocking the alpha-adrenergic effect, antagonistic to the serotonergic effect on the plexa level,[28] would thus favor the serotonergic effect and induce duodenal spasticity. This phenomenon would be evident in those segments of the intestine such as the duodenum and the distal colon which have a rich adrenergic activity. Finally, DHE besides stimulating central 5-HT postsynaptic receptors,[29, 30] is capable of directly stimulating the tryptamine receptors in the isolated stomach of rats.[31] These facts allow us to attribute to that drug both central and peripheral serotonergic-mediating actions. On the other hand, it has been shown that the alpha-adrenergic blocking agents but not the beta-adrenergic blocking agents, inhibited serotonergic raphe activity when administered systematically. Further, the inhibitory potency of these drugs on dorsal raphe nucleus activity correlates with reported central noradrenergic blocking efficacy.[32]

SUMMARY

DHE counteracts the gallbladder emptying induced by CCK. This effect would be due to a relaxation of the gallbladder in addition to an increase of duodenal tone. The alpha-adrenergic blockade produced by the drug would favor the beta-adrenergic and the serotonergic-cholinergic predominances at the gallbladder and the duodenum, respectively.

We speculate that a similar autonomic imbalance could be present in biliary hypokinesia, namely, serotonergic hyperactivity plus noradrenergic hypoactivity. With regard to this, we have accumulated enough data to assign to serotonin a weak alpha-agonistic role.[33, 34-36] 5-HT acting at the alpha-adrenoceptor levels, however, could blockade the action of noradrenaline, inducing a competitive inhibition. For the above mentioned reasons, it would be interesting to attempt in these subjects a therapeutic trial similar to that successfully performed in patients with headache and other depressive manifestations,[35] in whom the same autonomic imbalance was also postulated.

Finally, the high percentage of x-ray visualization of the gallbladder, 24 hours after DHE injection, would speak in favor of the long duration of the drug's effect.

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Rapid Diagnosis of Obstructive Jaundice Due to Pancreatic Abscess with Pancreaticobiliary Fistula

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A case of pancreatic abscess with pancreaticobiliary fistula manifesting as obstructive jaundice of occult etiology is presented. Diagnosis was made preoperatively by skinny needle percutaneous transhepatic cholangiography. In addition, a communication between the biliary tree and the pancreatic abscess cavity was demonstrated in the absence of previous biliary surgery or primary biliary tract disease. We feel this is the procedure of choice for emergency visualization of the biliary tree in a jaundiced patient where a surgically approachable lesion is suspected.

In any particular case the etiology of jaundice may prove a diagnostic puzzle. Biochemical, radiologic and endoscopic tests have evolved to simplify the clinician's dilemma. The problem of deepening jaundice, fever and abdominal pain is one, however, which does not permit the physician the time to employ multiple tests and prolonged evaluation. The work-up must be rapid and high yield. We discuss such a case and our recommendations.

CASE REPORT

A 45-year old white male, insulin dependent diabetic, was admitted to the Miami Veterans Administration Hospital on 19 September 1975 for the evaluation of abdominal pain, jaundice and fever. He had noted the onset of mid epigastric pain, radiating to his back, not relieved by antacids or aspirin two weeks prior to admission. The pain persisted but the patient was reluctant to go to the hospital. Four days prior to admission he had drenching night sweats and fevers. Two days prior to admission he noted dark urine and lighter stools. He began to have persistent nausea and vomiting. His wife noted his eyes were yellow. The patient had no history of alcohol abuse or biliary tract disease. His only medication was Insulin 40 units NPH subcutaneous daily.

Physical examination revealed an acutely ill, obese, icteric male. The temperature was 39° C, pulse 120 beats/minute and blood pressure 130/85. Funduscopic

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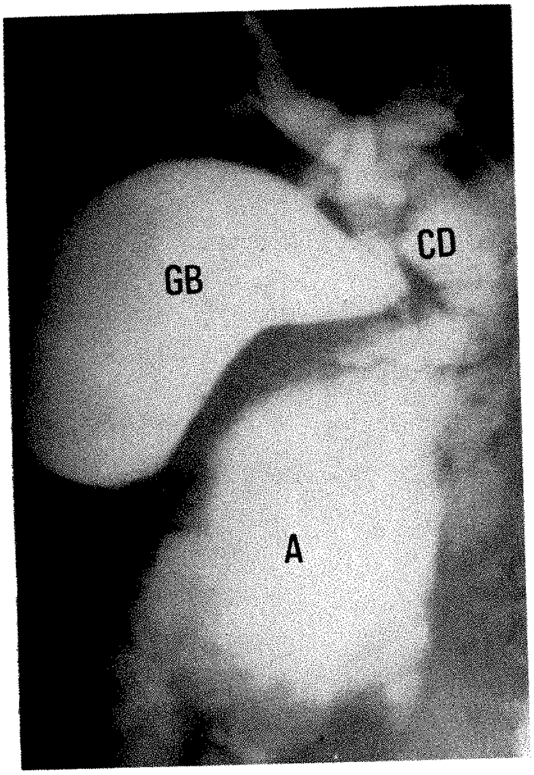

Fig. 1—This skinny needle percutaneous cholangiogram depicts the abscess cavity (A), communicating with a dilated common duct (CD) and biliary tree. The gallbladder (GB) is dilated and free of stones.

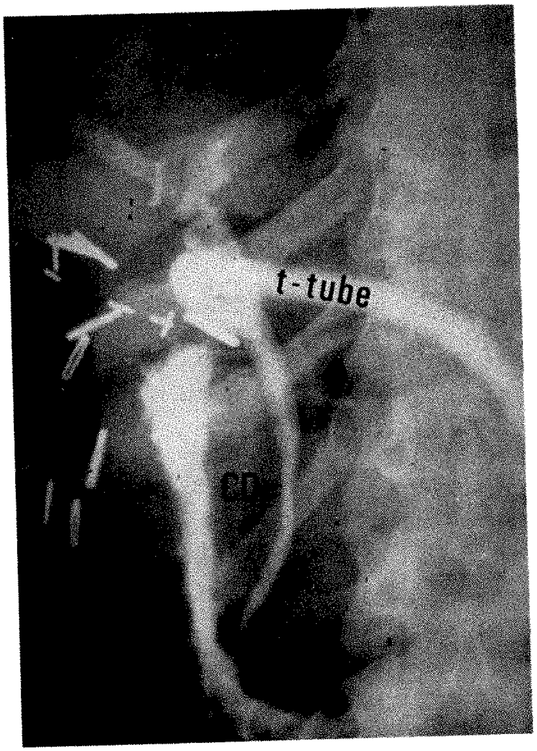

Fig. 2—The postoperative cholangiogram done through the T-tube demonstrates a non-dilated common duct (CD) and biliary tree. The dye readily enters the duodenum, also depicted.

examination revealed microaneurysms, scattered exudates, no papilledema or Roth spots. There were no spider angiomata. Bilateral rales were present at the lung bases. Cardiac examination was normal. The abdomen was diffusely tender with decreased bowel sounds but no rebound. The liver was palpable 3 cm. below the right costal margin in mid clavicular line, 11 cm. in total span. The spleen was not palpable and there was no ascites. Rectal examination was normal. Stool guaiac was negative. There was no lymphadenopathy or peripheral edema.

Initial laboratory data included a hemoglobin of 12.8 gm.%; hematocrit, 35%; white blood count, 13,000/cu. mm. with 24 bands, 60 segs, and 16 lymphs. Serum glucose was 305 mg./100 ml.; ketones were negative; BUN was 28 mg./100 ml., creatinine, 1.8 mg./100 ml.; calcium, 8.7 mg./100 ml. Total bilirubin was 14.6 mg./100 ml., direct was 13 mg./100 ml.; alkaline phosphatase was 290 I.U.; SGOT, 90 I.U., LDH, 320 u; total protein, 7 gm.% with an albumin of 2.6 gm.%. The serum amylase was 260 Somogyi units. The serum was not lipemic. Chest x-ray and KUB were unremarkable. ECG showed sinus tachycardia. Cultures were obtained and the patient was started on cleocin and gentamicin. Eight hours after admission a skinny needle transhepatic cholangiogram was attempted. On the first pass, injection of contrast medium filled an extrahepatic cavity and aspiration yielded pus. The second pass filled the gallbladder and biliary tree which was dilated (Fig. 1) and in communication with the abscess cavity.

The patient was taken to the operating room. At surgery a large abscess was found involving the head of the pancreas, compressing the duodenum and also extending into the lesser sac. A cholecystectomy, drainage of the retrogastric and subhepatic areas, and choledochotomy were done. T-tube cholangiography (Fig. 2) showed no stones in the common duct and a marked decrease in intrahepatic radicle size post-decompression. Postoperatively the patient's course was complicated by poor control of his diabetes, pneumonia, pancreaticocutaneous fistula and recurrent abscess. The patient had a cardiorespiratory arrest 20 days postoperatively and resuscitation was unsuccessful. Postmortem was not done.

COMMENT

Pancreatic abscess is a serious complication of pancreatitis. It occurs in approximately 4%[1, 2] of patients with pancreatitis and mortality has ranged from 37%[3] in patients undergoing surgical therapy to a universally fatal 100%[2, 4, 5] in cases without surgical intervention. The majority of pancreatic abscesses occur after pancreatitis due to alcoholism or biliary tract disease.[6] Other etiologies include abdominal trauma,[5] surgical manipulation,[7] infected pseudocyst[5] and vasculitis.[5] While the initial attack of pancreatitis may evolve rapidly into abscess, more commonly there is a ten-day to two-week interval where the patient improves and then deteriorates.[6] This is heralded by abdominal pain, fever, nausea, vomiting and occasionally a palpable mass.

Jaundice, usually mild and transient, occurs in up to 25% of patients with uncomplicated pancreatitis.[8] An expanding abscess cavity in the head of the pancreas may compress the duodenum and the common duct, causing obstructive jaundice.[5, 9] No figures are available for the frequency of this occurrence but it appears to be rare. In Altemeier's series[5] only one of 32 cases was jaundiced and in Evan's series[1] only one of 14. Other large series[2-4] of pancreatic abscess have failed to mention jaundice as a complication. Dalton reported a patient with pancreatic pseudocyst fistulizing into the biliary tree.[9] Pancreatic abscess has been seen after surgery on the biliary tree but pancreaticobiliary fistula was not noted as a presentation of pancreatic abscess.

Diagnostic aids available for the work-up of patients with obstructive jaundice are numerous. Recently, new technics: endoscopic retrograde cholangiopancreatography,[10] ultrasonography,[11] and skinny needle percutaneous transhepatic cholangiography[12, 13] have been employed with dramatic increase in presurgical diagnostic accuracy. While these tests sometimes complement each other, in other cases the information gained from subjecting the patient to multiple studies may be redundant and superfluous. In fact the physician in a medical center where all the tests are available must now ask himself "which test is *most* helpful? as well as "which will be helpful?"

In our case we were faced with the picture of obstructive jaundice in a very ill, septic, minimally cooperative patient with few clues as to the etiology. We were concerned that there was an underlying surgically approachable lesion. We did not have the time for an extensive work-up but still desired as much information as possible prior to subjecting the patient to laparotomy. We, therefore, elected to do transhepatic cholangiography for several reasons. This test has been shown to be a rapid, safe method to visualize the biliary tree.[12, 13] If obstruction is present, visualization of the dilated biliary tree is achieved almost 100% of the time.[12, 13] If there is visualization, obstruction is unlikely. This test requires only minimal cooperation from the patient. It requires no extensive preparation. As was evident in our case the surgeon was presented with a good idea of what he was to find as well as anatomic delineation of the lesions.

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Communication from Abroad

Pancreatic Excretion Test and Barrier Hypothesis in Progression of Chronic Pancreatitis

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Simultaneous data of the pancreozymin-secretin test and the pancreatic excretion test with 5,5-dimethyl-2,4-oxazolidinedione (DMO) were reported for 50 patients with chronic pancreatitis. The pancreozymin-secretin test was abnormal in 90% of the patients, while the pancreatic DMO excretion test showed abnormality in 100% of the patients.

The dynamic process of pancreatic excretory dysfunction is discussed. Over 60% of patients with low to moderate grade chronic pancreatitis showed a discordant pattern of decreased DMO output with normal bicarbonate concentration or normal volume flow. Approximately 96% of patients with advanced grade chronic pancreatitis had a excretory pattern of decreased DMO output with low bicarbonate concentration and decreased volume flow. These findings may further develop a barrier hypothesis in chronic pancreatitis. In the early stage of chronic pancreatitis, when functional capacity of the duct is preserved fairly well, the extraductal barrier to the rapid DMO diffusion into the ducts (diffusion barrier) may be primarily responsible for impaired pancreatic DMO excretion. With progression of chronic pancreatitis, the intraductal barrier (outflow barrier) may become pronounced and precipitate pancreatic excretory dysfunction for DMO. The concept of pancreatic barriers may well serve to systematize major histologic alterations observed in chronic pancreatitis.

INTRODUCTION

The substance of 5,5-dimethyl-2,4-oxazolidinedione (DMO) is a weak organic acid with a molecular weight of 129.1, and an ionization exponent (pK′) of 6.13 at 37 C.[1] The human pancreas, in a normal or diseased state, is capable of excreting the compound.[2-4] In previous reports we have described that the pancreatic DMO excretion test may well become an effective tool for detecting early stages of pancreatic disease including chronic pancreatitis and pancreatic carcinoma.[3, 4] In chronic pancreatitis, of whatever etiology, pancreatic excretion of DMO declines as the inflammation progresses towards the final stage.[3] We have previously advanced the hypothesis that in early stages of chronic pancreatitis, excretory impairment of pancreatic DMO

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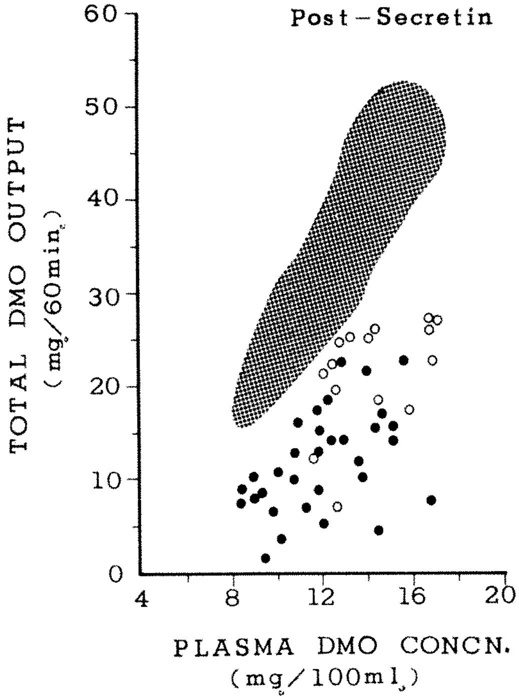

Fig. 1—Relationship between total DMO output and plasma DMO concentration in the postsecretin 60-minute period in 50 patients with chronic pancreatitis. Stippled area, which outlines the normal relationship, was determined by inspection. ● pancreatolithiasis, O histologic proof of chronic pancreatitis.

would be primarily due to impaired DMO diffusion into pancreatic ducts (diffusion barrier) and later it would result not only from the diffusion barrier but from disturbed DMO outflow in the ducts (outflow barrier).[3, 4]

This study is an extension of our previous work on pancreatic DMO excretion in a normal and diseased state. An attempt was made to evaluate the comparative diagnostic value of the pancreozymin-secretin test and the pancreatic DMO excretion test and to give further support to the hypothesis of pancreatic barriers in patients with different severity of chronic pancreatitis.

MATERIALS AND METHODS

Fifty patients (42 males and eight females) with chronic pancreatitis were selected for this study. They consisted of 35 patients with pancreatolithiasis and 15 patients with histologic evidence of chronic inflammation. Their ages ranged from 21-72 years with a mean of 49. The informed consent from patients was obtained prior to examinations.

The diagnosis of pancreatolithiasis was made from plain radiological films of the abdomen. The endoscopic retrograde pancreatography, performed on 21 patients with pancreatolothiasis, showed marked dilatation or irregularity of the ducts and intraductal calculi of varying sizes. In the histological diagnosis group, there were eight patients with cholelithiasis; three patients with pancreatic cyst and four patients with miscellaneous diseases such as idiopathic choledochal cyst, liver cyst, gastric carcinoma, and leiomyosarcoma of the duodenum. Histologic studies of the pancreas were performed on resected or biopsy specimens obtained at operation. Histologic severity of lesions was graded into three degrees on the basis of extent and severity of fibrosis associated with varying degrees of cell infiltration. The minimal grade was characterized by perilobular fibrosis, the moderate grade by intralobular fibrosis and the advanced grade by severe and extensive fibrosis which replaced or surrounded individual acini or groups of acini. This grading was based principally on histological diagnostic criteria for chronic pancreatitis proposed by the Japanese Pancreatic Research Association.[5] In 15 patients of this group, the minimal grade was found in eight patients, the moderate grade in four patients and the advanced grade in three patients. Alcohol ingestion seemed to be a main causative factor in 28 of 34 male patients with pancreatolithiasis and in three

TABLE I

INCIDENCE OF ABNORMAL FINDINGS IN PANCREOZYMIN-SECRETIN TEST, PANCREATIC DMO EXCRETION TEST AND 50 GM. GLUCOSE TOLERANCE TEST IN 50 PATIENTS WITH CHRONIC PANCREATITIS[*]

	Pancreozymin-secretin test[†]					DMO excretion test[‡]			50 gm. OGTT	
	N	Normal	+	++	+++	Normal	Standard DMO output	Max. J/P ratio	Non-diabetic	Diabetic
Chronic pancreatitis	50	5 (10)	6 (12)	14 (28)	25 (50)	0 (0)	50 (100)	33 (66)	24 (48)	26 (52)
Calcific	35	1 (3)	1 (3)	8 (23)	25 (71)	0 (0)	35 (100)	30 (86)	11 (31)	24 (69)
Non-calcific (with histologic proof)	15	4 (27)	5 (33)	6 (40)	0 (0)	0 (0)	15 (100)	3 (20)	13 (87)	2 (13)
Minimal	8	2	3	3	0	0	8	1	7	1
Moderate	4	1	1	2	0	0	4	1	4	0
Advanced	3	1	1	1	0	0	3	1	2	1

[*] Number in the parenthesis indicates percentage.

[†] Abnormality of the pancreozymin-secretin test was expressed as +, ++ and +++ according to the number of abnormal parameters.

[‡] Standard DMO output indicates the total DMO output corrected to a level of 10 mg./100 ml. of plasma DMO. Maximal J/P ratio represents the maximal value of duodenal juice/plasma concentration ratio for DMO in the postsecretin 30- to 60-minute periods.

of 15 patients with noncalcific chronic pancreatitis.

The DMO excretion test was performed concomitantly with the pancreozymin-secretin test. Details of the procedure have been described previously.[2] All patients received 0.45 gm. of 3,5,5-trimethyl-2,4-oxazolidinedione (trimethadione, precursor of DMO) three times daily for three consecutive days. The pancreozymin-secretin test, partially modified in our laboratory, was performed four days after the last dose of the drug. A Bartelheimer double balloon tube[6] was placed in the third portion of the duodenum under fluoroscopic observation. After two 10-minute control samples of duodenal aspirates were obtained, pancreozymin (Boots, Nottingham, England) in a dose of 1 Crick-Harper-Raper (CHR) unit/kg. body weight was injected intravenously and three samples of duodenal aspirate were collected at 10-minute intervals. Six 10-minute collections of duodenal samples then followed the intravenous administration of 1 CHR unit/kg. body weight of secretin (Boots). Blood samples were taken by heparinized syringes immediately before the injection of each hormone and 60 minutes after secretin administration.

DMO concentration in duodenal content and plasma was measured by the modified method of Butler using a Shimadzu MPS-50L spectrophotometer.[1, 7] Bicarbonate concentration in the aspirate was determined by the titrimetric method with a Radiometer TTT 1c autotitrator[8] and amylase activity by Caraway's iodometric method.[9]

The oral glucose tolerance test (GTT) was done in all patients. After an overnight fast, blood was drawn before oral administration of 50 gm. glucose and at intervals of 30, 60, 90 and 120 minutes thereafter. Blood glucose was measured with the autoanalyzer. The GTT was assessed according to the criteria published by the Japanese Diabetes Association.[10]

Sixty-seven healthy subjects, ranging in age from 18-81 years (mean 44 years), served as normal controls.

Statistical significance was evaluated by application of the nonpaired "t" test. The null hypothesis was rejected at the 5% level.

RESULTS

Relationship between total DMO output and plasma DMO concentration:—In this study as well as in previous series,[4] DMO output of duodenal contents in each subject was assessed only in the postsecretin 60-minute period. Figure 1 shows the relationship between total DMO output and plasma DMO concentration in 35 patients with pancreatolithiasis and 15 patients with histologic proof of chronic pancreatitis. The stippled area, which outlines the normal relationship, was determined by inspection. Plasma DMO concentration in the patients varied within the range observed in healthy subjects (range: 8.4-17.0 mg./100 ml.). Total DMO output of each patient was plotted below the lower limit of normal defined by inspection.

Comparative diagnostic value of pancreozymin-secretin test and pancreatic DMO excretion test:—Table I shows abnormality of the pancreozymin-secretin test, DMO excretion test and 50 gm. GTT in 50 patients with chronic pancreatitis. The parameters for the assessment of the pancreozymin-secretin test comprised: 1. total volume after secretin administration (ml./60 min.); 2. maximal bicarbonate concentration (mEq./l.) and total amylase output after pancreozymin-secretin administration (unit/90 min.). The parameters which were used in the assessment of the DMO excretion test included: 1. stand-

TABLE II

DATA ON PANCREOZYMIN-SECRETIN TEST AND PANCREATIC DMO EXCRETION TEST IN 67 NORMAL SUBJECTS AND 50 PATIENTS WITH DIFFERENT GRADE CHRONIC PANCREATITIS[*]

	Pancreozymin-secretin test[**]				DMO excretion test[***]	
	N	Volume (ml./60 min.)	Maximal bicarbonate concentration (mEq./l.)	Amylase output (units × 10^3/90 min.)	Standard DMO output (mg./60 min.)	Maximal J/P ratio
Control	67	199.0 ± 35.8	100.0 ± 10.9	193.7 ± 61.6	35.0 ± 3.8	1.44 ± 0.15
Chronic pancreatitis	50	105.6 ± 35.2†	53.7 ± 23.8†	55.2 ± 45.5†	20.6 ± 4.3†	1.10 ± 0.31†
Low grade	10	131.2 ± 36.1†	78.3 ± 15.5†	105.7 ± 37.6†	22.8 ± 3.3†	1.32 ± 0.28†
Moderate grade	12	124.2 ± 28.3†	65.5 ± 15.0†	77.4 ± 29.8†	22.7 ± 2.9†	1.21 ± 0.25†
Advanced grade	28	88.5 ± 28.2†	39.8 ± 19.1†	28.2 ± 31.7†	18.9 ± 4.4†	0.98 ± 0.31†

[*] Values represent means ± SD. Significant differences from controls at 0.001% level are represented by daggers.

[**] Amylase output in the postpancreozymin-secretin 90-minute period.

[***] Significance of standard DMO output and maximal J/P ratio as in Table I.

ard DMO output after secretin stimulation (mg./60 min.) and 2. maximal concentration ratio of duodenal juice/plasma in the postsecretin 30- to 60-minute period (maximal J/P ratio). Standard DMO output was defined as the output corrected to a level of 10 mg./100 ml. of plasma DMO in order to present a certain basis for comparison of data obtained. In the present study, it was calculated in much the same way as described previously.[4] The lower limit of normal and coefficient of variation for each parameter were also reported previously.[4] In the table, abnormality of the pancreozymin-secretin test was expressed as +, ++ and +++, according to the number of abnormal parameters. In the entire group of chronic pancreatitis, 90% of the patients were abnormal in more than one parameter in the pancreozymin-secretin test. Abnormality of the pancreozymin-secretin test was more pronounced in patients with pancreatolithiasis than with noncalcific chronic pancreatitis. In pancreatolithiasis, 94% of the patients were abnormal in more than two parameters and only 3% of the patients showed normal results in the pancreozymin-secretin test. In noncalcific chronic pancreatitis, histologic abnormalities did not necessarily correspond to functional abnormalities demonstrated by the pancreozymin-secretin test. Four patients of this group (27%) had normal findings in the test and only three of seven patients with moderate to advanced histologic severity showed abnormality in more than two parameters. The percentage of abnormality for standard DMO output and maximal J/P ratio in the entire group was 100% and 66%, respectively. Abnormality of maximal J/P ratio was more prominent in patients with pancreatolithiasis than with noncalcific chronic pancreatitis. In the 50 gm. GTT, 52% of the patients were diabetic. The incidence of diabetes mellitus was much higher in patients with pancreatolithiasis than in those with noncalcific chronic pancreatitis.

Redivision of the patients by morphological and functional abnormalities: According to morphological and exocrine functional abnormalities observed, 50 patients with chronic pancreatitis were redivided into three groups: low grade in 10, moderate grade in 12 and advanced grade in 28. The low grade chronic pancreatitis group consisted of eight patients with minimal histologic severity and two patients with pancreatolithiasis who showed the normal or only one abnormal finding in the pancreozymin-secretin test. The moderate grade chronic pancreatitis group was composed of four patients with moderate histologic severity and eight patients with pancreatolithiasis who had two abnormal findings in the pancreozymin-secretin test. The advanced grade chronic pancreatitis group comprised three patients with advanced histologic severity and 25 patients with pancreatolithiasis who showed abnormality in all parameters of the pancreozymin-secretin test. Table II summarizes the statistical analyses of data of the pancreozymin-secretin test and the DMO excretion test in 67 healthy subjects and 50 patients with different grade chronic pancreatitis. The mean value for each parameter of the tests was significantly reduced in chronic pancreatitis ($P < 0.001$) and gradually decreased with increasing severity of the disease.

Relationship between standard DMO output and maximal bicarbonate concentration:—In order to detect a functional cause of pancreatic excretory dysfunction associated with progression of chronic pancreatitis, the relationship between standard DMO output and maximal bicarbonate concentration was studied in patients with different grade chronic pancreatitis (Fig. 2). The horizontal and vertical lines in the

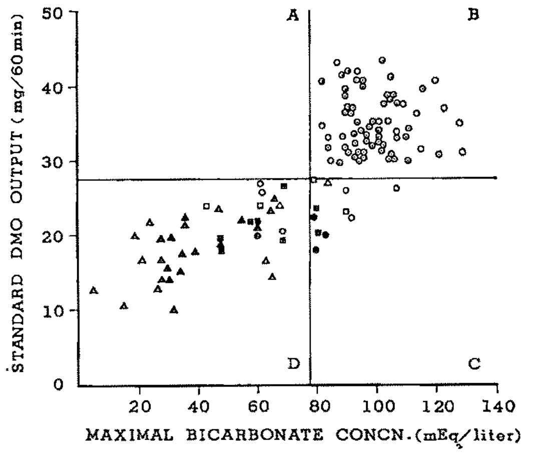

Fig. 2—Relationship between standard DMO output and maximal bicarbonate concentration in 67 normal subjects and 50 patients with different grade chronic pancreatitis. Horizontal and vertical lines represent the normal lower limit of standard DMO output and maximal bicarbonate concentration, respectively. Significance of standard DMO output as in Table I. ⊙ normal, ○ ● low grade chronic pancreatitis, □ ■ moderate grade chronic pancreatitis, △ ▲ advanced grade chronic pancreatitis. Closed signs indicate a decrease in volume.

figure, representing the lower limit of normal for standard DMO output and maximal bicarbonate concentration, respectively, yielded four sections from A to D. Section A signified normal standard DMO output with low maximal bicarbonate concentration; section B, normal standard DMO output with normal maximal bicarbonate concentration; section C, decreased standard DMO output with normal maximal bicarbonate concentration and section D, decreased standard DMO output with low maximal bicarbonate concentration. The closed signs in the figure represent a decrease in volume. There was no overlapping distribution between normal subjects and patients with chronic pancreatitis. The normal subjects were distributed only in section B, while the patients dispersed in sections C and D. Sixty per cent of the low grade of patients were in section C and 67% of the moderate grade and 96% of the advanced grade of patients were in section D. The distribution of the patients, although overlapping each other, shifted from section C to section D with an increase in severity of chronic pancreatitis. The incidence of abnormally low volume flow in the patients was increased as chronic pancreatitis progressed towards the advanced grade: low grade in 60%, moderate grade in 67% and advanced grade in 93%.

Comment

The antiepileptic agent, trimethadione, is converted by metabolic N-demethylation to DMO.[11] Waddell and Butler[12] have reported that the compound is almost ideal for the indirect measurement of intracellular pH. We, in an effort to diagnose chronic pancreatic disease early, have recently developed the new technic for detecting another functional profile of the pancreas, i.e. pancreatic excretory function with DMO.

In general, a diagnostic accuracy of approximately 90% has been reported with secretory tests via duodenal intubation.[13] Although the number of the patients examined, when compared with that presented by Dreiling in the standard secretin test,[14] was far smaller, the results obtained indicated that the pancreatic DMO excretion test was superior to the pancreozymin-secretin test in the diagnosis of chronic pancreatitis, particularly minimal to moderate grade chronic pancreatitis. Probably with extended studies, this new test will correlate very closely with the standard secretin test and attain a greater degree of accuracy in the diagnosis of chronic pancreatitis. In the previous study, we reported that the recovery of duodenal DMO seemed complete or nearly complete even if the gastric juice happened to contaminate the pancreatic juice in considerable degree.[3] The

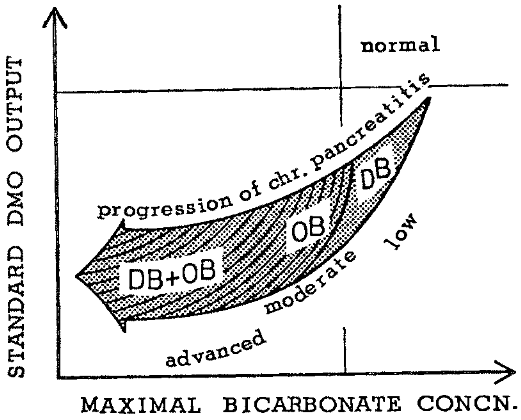

Fig. 3—Schematic illustration of development of pancreatic barriers with progression of chronic pancreatitis. DB and OB indicate diffusion barrier and outflow barrier, respectively. Significance of standard DMO output as in Table I.

new test, therefore, is of diagnostic usefulness to corroborate existence of chronic pancreatitis in patients showing low bicarbonate concentration. In this study, no patients gave a secretory pattern of hypersecretion which might be characteristic of minimal grade chronic pancreatitis.[15, 16]

In two-thirds of patients with noncalcific chronic pancreatitis, histologic studies of the pancreas were performed on small biopsy specimens obtained largely from the pancreatic body. Since histologic features of chronic pancreatitis are characterized by sclerosis with exocrine parenchymal destruction which may be focal, segmental, or diffuse,[17] discrepancy, as observed in the present study, may exist to some extent between histologic findings and results of the pancreozymin-secretin test. The present results suggest that with further studies the pancreatic DMO excretion test may well cover a lack of association between morphological and functional findings.

In the present study, 50 patients with chronic pancreatitis were redivided into three groups in order to detect the dynamic process of excretory impairment of pancreatic DMO. Since DMO is a weak organic acid with a pK′ nearly equal to that of carbonic acid, it can diffuse rapidly to the pancreatic juice according to its pH gradient under normal circumstances. The pH of the juice, as expected from the Henderson-Hasselbalch equation, is regulated primarily by bicarbonate concentration in the juice because buffers other than the bicarbonate-carbonic acid system are extremely low. We preferred to investigate the dynamic process of pancreatic excretory dysfunction in relation to bicarbonate concentration rather than volume and enzyme secretions for the above reasons.

As to impairment of pancreatic DMO excretion in chronic pancreatitis, we have previously supposed "pancreatic barriers"; one is the diffusion barrier and another is the outflow barrier.[3, 4] The development of pancreatic barriers with progression of chronic pancreatitis is schematically illustrated in Figure 3, where DB and OB indicate the diffusion and outflow barriers, respectively. This figure was made from both the relationship between standard DMO output and maximal bicarbonate concentration as shown in Figure 2 and the data of the pancreozymin-secretin and DMO excretion tests as given in Table II. In low grade chronic pancreatitis, the functional capacity of the ductal cells including bicarbonate and water secretions was preserved fairly well (Table II), indicating that the extraductal barrier to the rapid DMO diffusion into the ducts (diffusion barrier) might be primarily responsible for a decrease in pancreatic DMO excretion in the early stages of chronic pancreatitis. With progression of chronic pancreatitis, the capacity of the ductal function, as shown in Table II, was progressively reduced. It seems reasonable to assume that as chronic pancreatitis progresses towards the advanced stage, the intraductal barrier to the smooth outflow of DMO (outflow barrier) may become pronounced, and further precipitate pancreatic excretory dysfunction for DMO. That is, the diffusion barrier may precede the outflow barrier in progression of chronic pancreatitis. In far advanced chronic pancreatitis, both barriers may be responsible equivalently or unequivalently for highly impaired pancreatic excretion of DMO.

The intrapancreatic passway of DMO is not known yet. The concept of pancreatic barriers, however, may well serve for systematic arrangement of major histologic alterations observed in chronic pancreatitis. The diffusion barrier may include various histologic alterations, such as perilobular or intralobular fibrosis, residual area of necrosis, thickening of basement membranes surrounding endothelial, ductal and acinar cells and interstitial exudate.[17-21] The outflow barrier may include some intraductal alterations, such as hyperplasia of the mucus-producing cells sometimes associated with papillary infolding of the epithelium, deposits of epithelial debris and mucus, and calculi.[17-21] We agree with Baggenstoss[19] and Sarles and Sahel[21] that fibrosis is perilobular at first and then intralobular. According to Berens, et al,[22] and Sarles, et al,[18] the duct of Wirsung is normal in the early stage but later dilated as a result of obstruction either by stenosis or by stones. We consider that these observations may give histologic support to the hypothesis of pancreatic barriers. Further studies under light and electron microscope are being undertaken to strengthen the hypothesis.

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Inhibition of Ethionine Pancreatitis in the Rabbit by DL-β-3 Thienylalanine Pretreatment

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Beta-3 thienylalanine, an inhibitor of zymogen formation, was studied in the experimental model of ethionine pancreatitis in the rabbit. β-3TA pretreated and nonpretreated rabbits were given ethionine for six days and controls were given chow only. Animals were killed and serum amylase values determined. Pancreatic tissue was studied by light and electron microscopy. β-3TA pretreated rabbits on ethionine showed normal amylase values, while those receiving only ethionine showed high values. Microscopic examination showed severe pancreatitis in the nonpretreated group but only mild vacuolization of cells in the β-3TA pretreated animals. Electron microscopy demonstrated integrity of rough endoplasmic reticulum in pretreated animals and severe distortion of cytoplasmic organelles in nonpretreated animals.

Since 1950, ethionine has been used as a model of pancreatic injury, although the mechanism of the injury remains obscure.[1, 2] Beta-3-thienylalanine (β-3TA), an analogue of the amino acid phenylalanine inhibits zymogen granule formation in pancreatic cells of rats[3] and has been shown to prevent drug-induced pancreatitis in the rat model of ethionine pancreatitis.[4] We have attempted to confirm and extend in rabbits these earlier observations obtained in rats.

Materials and Methods

Twenty-four male, white California rabbits each weighing about 2,000 gm. were divided into three groups. Eight controls received regular chow diet. The second group was pretreated for three days with β-3TA, in a single dose 3 × equimolar to phenylalanine (250 mg./kg). This was followed by an equimolar dose daily for six days together with ethionine (140 mg./kg.), given intraperitoneally. The third group received the same amount of ethionine as the rabbits in group two but without β-3TA. After six days on ethionine, the rabbits were killed by stunning. Serum amylase was determined by the Coleman amylase-lipase analyzer (T-332 methods file).[5] Samples of pancreas were removed for pathologic study with hematoxylin and eosin and Wilder's reticulum stains.

The light microscopy slides were coded and read as unknowns by the pathologist (R.A.G.) Pathologic findings were categorized and graded in severity from 1 plus to 4 plus. Electron microscopy was also done in order to appraise the degree of zymogen suppression, changes in rough endoplasmic reticulum and the development of autophagic vacuoles.

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TABLE I

PATHOLOGIC CHANGES

Pathology class	Untreated controls	β-3TA + ethionine*	Ethionine**
Inflammation	0/8	1/6	5/6
Fat necrosis	0/8	0/6	1/6
Edema	0/8	1/6	5/6
Hemorrhage	0/8	1/6	5/6
Reticulin	0/8	0/6	5/6
Zymogen loss	0/8	3/6	6/6
Acinar vacuoles	0/8	3/6	6/6

* Damage of 1+ and 2+

** Damage of 2+ to 4+

(Two animals in groups II and III died before the seventh day.)

(Number of animals showing pathology over number of animals observed.)

1+ – mild, 2+ – moderate, 3+ – severe, 4+ – very severe pathologic change.

TABLE II

SERUM AMYLASE DATA

	Control	Ethionine	β-3TA + ethionine
	220	890	261
	240	242	233
	245	700	244
	243	386	261
	185	1610	159
	252		167
	193		225
	218		
Sample mean	224.5	765.6	221.4
Std. error of mean	8.84	239.9	15.9
Std. deviation	24.997	536.4	42.1
Sample size	8	5	7

"t" tests 1. Control-vs.-ethionine means
$t(12) = 2.9286$, $P < .01$ (one tail).
2. Control-vs.-β-3TA + ethionine means
$t(13) = 0.1746$, $P > .8$ (two tail).

RESULTS

Untreated controls exhibited no pathological changes. Pathological changes (Table I) observed with ethionine were milder or absent when β-3TA was given. Fat necrosis, not frequently observed at the level of ethionine dosage used here, was seen in one specimen. Electron microscopy was normal in control animals. Animals pretreated with β-3TA before and with ethionine showed few changes and the rough endoplasmic reticulum was preserved (Fig. 1). In contrast, group III animals (ethionine only) showed marked dilation of cisternae of the rough endoplasmic reticulum, severe disorganization of the cytoplasm, and nuclear distortion, as well as possible rupture of zymogens (Fig. 2).

Serum amylase values obtained after the sixth day of ethionine were normal in controls and β-3TA pretreated animals ($P = NS$) but were markedly elevated in nonpretreated animals (Table II). Means were 224 units in controls, 221 in β-3TA pretreated and 765 units of amylase per 100 ml. in nonpretreated animals ($P < 0.01$ comparing the last group with the other two groups).

COMMENT

Ethionine pancreatitis has remained an obscure entity, although studies of cellular amino acids levels and enzyme activities have demonstrated increased amounts of both after ethionine feeding for 24 hours. After longer contained feeding of ethionine, a fall in enzyme concentration occurs in the unstimulated gland and delayed enzyme excretion in the stimulated gland, as a result of acinar damage.[9] Earlier experiments have shown initially increased zymogens in the apices of acinar cells, followed by a decrease accompanied by degeneration and damage to the cells.[1-4] Our electron microscopic study in this experiment was done at a later stage in the pancreatitis process, showing marked enlargement of cisternae of the rough endoplasmic reticulum and nuclear changes. These changes were largely prevented by β-3TA, an inhibitor of zymogen synthesis, even in the presence of phenylalanine in the diet.

Autophagocytosis of pancreatic cells has been induced by ethionine as well as other inducers such as neutral red, vinblastine, puromycine and cadmium ions and prevented by cyclohexamide which appears to prevent formation of limiting membranes of autophagic vacuoles and preservation of RER.[6] Such experiments have been conducted over a 60-minute period with other methods than ours.

Ethionine appears to exert its toxic effects upon the pancreatic acinar cell after zymogen synthesis has occurred. This may be the result of either stimulation of autophagic vacuoles which may in turn rupture, or by an effect upon zymogens themselves causing them to rupture leading in either case to a condition of autophagocytosis. These effects may occur even with the addition of methionine in the diet. Ethionine producing bacteria occur in mammalian intestinal tracts and conceivably in those of man. Further investigations into its presence and action are indicated because of a possible role in human pathology. The benefit of β-3TA in preventing one form of animal pancreatitis is a consistent observation. An antimetabolite of this type may be useful in the treatment of this and other forms of pancreatic injury.

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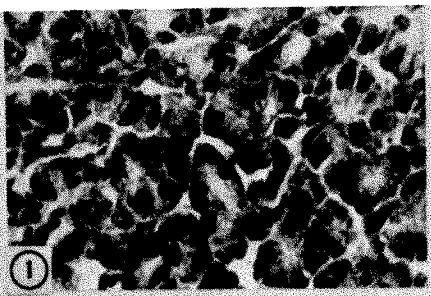

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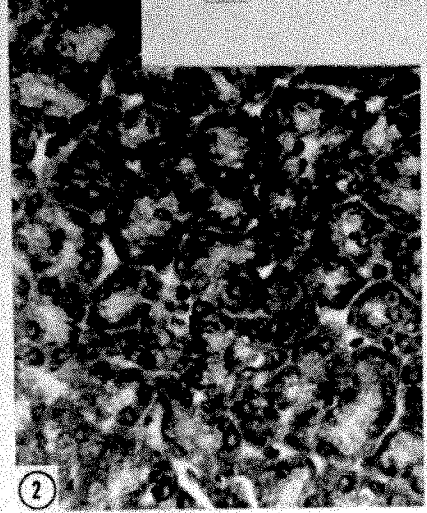

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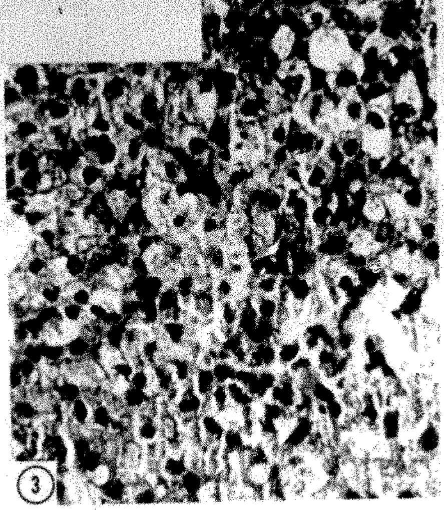

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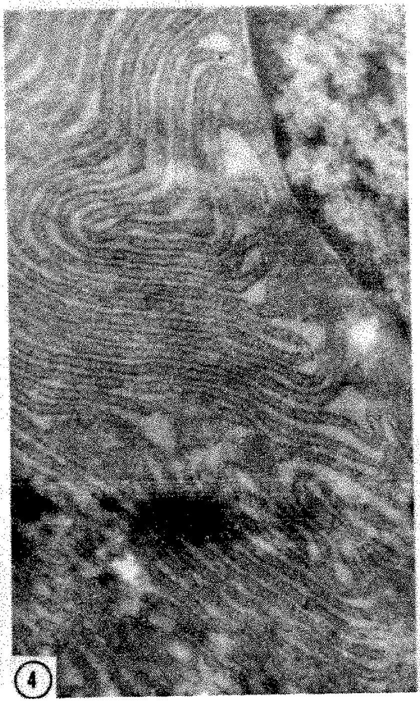

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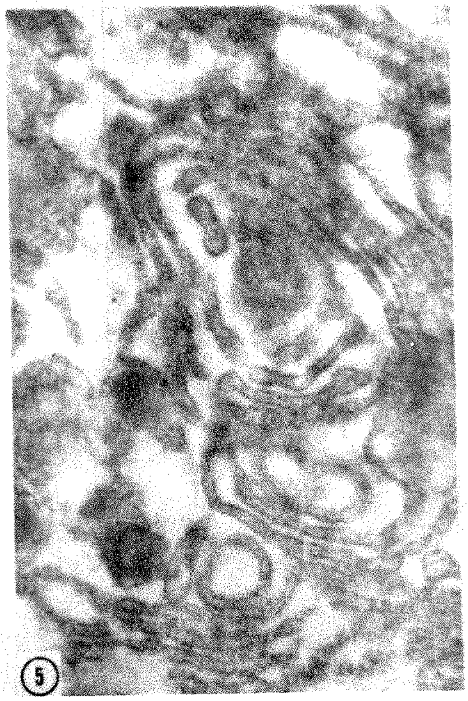

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Fig. 1—Normal control rabbit pancreas fed chow diet 10 days. Note normal acinar, lobular architecture and abundant zymogen material (Hematoxylin and eosin, original magnification x400)

Fig. 2—Typical pancreas of rabbit pretreated with β-3TA plus ethionine. Note preservation of acinar architecture, lack of nuclear pyknosis and absence of inflammation (Hematoxylin and eosin, original magnification x400).

Fig. 3—Typical pancreas of rabbit receiving ethionine without β-3TA showing loss of acinar architecture and disruption of normal lobular pattern. (Hematoxylin and eosin, original magnification x400).

Fig. 4—Pancreas of rabbit receiving ethionine after pretreatment with β-3TA. The nucleus and rough endoplasmic reticulum appear relatively intact (EM, original magnification x24,000).

Fig. 5—Pancreas of rabbit on ethionine without β-3TA pretreatment. There is disruption and distortion of the rough endoplasmic reticulum and an accumulation of protein material (EM, original magnification x24,000).

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Spontaneous Umbilical Hernia Rupture

A REPORT OF THREE CASES

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Three cases of spontaneous umbilical hernia rupture in patients with alcoholic liver disease and ascites are reported. Eighteen cases have been previously reported in the literature. These 21 cases are reviewed in an attempt to determine precipitating events, prognostic factors, complications, and the results of therapy. All patients had significant ascites prior to umbilical rupture. Ulceration of the umbilicus prior to rupture was common (81%). The subsequent presence of peritonitis, hypotension, renal failure, gastrointestinal hemorrhage or hepatic coma was associated with significant mortality (80%). All patients with a serum albumin above 2.4 gm./dl. survived. There were no survivors in those patients who did not receive surgical treatment. Based upon the outcome of these 21 patients optimal treatment of this disorder would seem to be early surgical repair of the umbilical hernia, appropriate fluid and electrolyte replacement, antiobiotics and measures to reduce intraabdominal pressure.

Spontaneous abdominal paracentesis due to umbilical hernia rupture is an uncommon but frequently fatal complication of ascites. Since Stein and Strauss[1] described umbilical hernia rupture in a patient with cirrhosis and ascites in 1951, there have been 17 additional cases reported.[2-13] Although spontaneous umbilical hernia rupture is not common, it represents a serious complication associated with a high mortality. In spite of the availability of potent diuretics, this complication still occurs. We have recently encountered three cases of spontaneous umbilical hernia rupture associated with ascites in alcoholic patients with cirrhosis.

CASE REPORTS

Case 1:—A 46-year old male was admitted to the hospital complaining of abdominal distention, protrusion of his umbilicus and a 9.45 kg. weight gain over the preceding month. The patient had had a heavy intake of alcohol for over 20 years. Four years prior to admission, hepatomegaly and abnormal liver function tests were first noted. A liver biopsy at that time revealed cirrhosis. Ascites associated with an umbilical hernia had been present for two years prior to admission.

Physical examination at the time of admission revealed marked ascites and a grapefruit-sized ulcerated umbilical hernia. Pedal edema, gynecomastia, spider angiomata and multiple ecchymoses of the trunk and extremities were also present.

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Laboratory studies were consistent with cirrhosis of the liver.

On the second hospital day, an abdominal paracentesis was performed with the removal of 2 liters of fluid. Later that day, following an episode of coughing, the umbilical hernia ruptured with the sudden loss of approximately 8 liters of fluid. Although the patient complained of weakness, the vital signs remained stable. The following day, the patient suddenly lost approximately 4 more liters of fluid from his umbilical wound. The wound was closed with sutures and pressure dressings were applied. His subsequent course was complicated by continued ascites formation, wound dehiscence and peristent umbilical drainage. He lost a total of 18.45 kg. Three weeks following admission, an end-to-side portacaval shunt and an umbilical herniorrhaphy were performed without incident. The patient convalesced satisfactorily and was discharged on a low sodium diet and diuretics. Three years following rupture of his umbilical hernia he died of progressive hepatic insufficiency and renal failure.

Case 2:—A 55-year old male was admitted to the hospital for treatment of hepatic coma. The patient had used alcohol excessively for many years. A diagnosis of cirrhosis had been made three years previously. One year prior to admission transesophageal ligation of bleeding esophageal varices had been performed at another hospital. Shortly thereafter, acites developed and a large umbilical hernia was first noted. The patient spontaneously began leaking fluid from his umbilicus 48 hours prior to admission. He developed increasing lethargy and was brought to the hospital.

Physical examination revealed a cachectic dehydrated male who responded only to painful stimuli. Vital signs were normal. A leaking ulcerated umbilical hernia was present. Liver and spleen were enlarged and there was moderate edema of the legs. The diagnosis of hepatic cirrhosis was supported by the laboratory tests of liver function.

The patient was treated with intravenous salt-poor albumin and other parenteral fluids, a low protein diet, oral neomycin and systemic antibiotics. His sensorium completely cleared in 48 hours. The drainage from his umbilical wound stopped but ascites started to reaccumulate. His subsequent course was progressively downhill. Although, no further umbilical drainage occurred, he developed increasing ascites, hepatic coma, cardiac arrhythmias, hypotension, renal failure and pneumonia and died four weeks after admission.

Case 3:—A 64-year old male was admitted to the hospital complaining of fluid pouring from his abdomen. The patient had had a heavy alcoholic intake during the past 30 years. During the year preceding admission, he had developed persistent ascites. Abdominal distention had progressively increased and an enlarging umbilical hernia had been noted by the patient. One week prior to admission, slow seepage of clear yellow fluid from the umbilical hernia had begun. On the day of admission, while he was quietly lying in bed, there was a sudden outpouring of fluid from his umbilicus resulting in an acute loss of approximately 12.6 kg. of body weight.

On physical examination the patient was alert and oriented and in no apparent distress. The vital signs were normal without orthostatic changes. The abdomen was flaccid and revealed an ulcerated umbilical hernia. Hepatosplenomegaly was present. Laboratory examination supported the diagnosis of cirrhosis.

The following day repair of the umbilical hernia was carried out under general anesthesia. The immediate postoperative course was uneventful except for the reformation of ascites. The patient was treated with a low sodium diet and diuretics and was able to leave the hospital in 10 days. One week later, he was readmitted to the hospital with hepatic encephalopathy and oliguria. His hospital course was complicated by the development of upper gastrointestinal bleeding from both esophageal and gastric varices. After a prolonged and difficult course, his condition stabilized and he was discharged from the hospital. The patient has continued to do well and has remained free of ascites and hepatic encephalopathy 8 months following umbilical hernia rupture.

COMMENT

Spontaneous umbilical hernia rupture in adults is characteristically seen in patients with chronic liver disease and ascites. Of the 25 cases of adult umbilical hernia rupture reported during this century,[1-19] 18 were associated with chronic liver disease.[1-13] These 18 cases plus our three form the basis of this report.

Twenty of these 21 cases of umbilical rupture in patients with chronic liver disease and ascites had pre-existing umbilical hernias prior to rupture. In one case, the presence or absence of a prior hernia was not mentioned. Frequently described predisposing conditions included trauma, infection and pressure necrosis. It is of interest that ulceration of the hernia was described in 13 (81%) of the 16 cases in which the appearance of the umbilicus was known prior to rupture.

Rupture of the umbilical hernia was spontaneous in 15 (71%) of the 21 cases. In only six cases was a precipitating event prior to rupture described. Five of these events were related to maneuvers which would increase intra-abdominal pressure. These included the removal of an abdominal binder and assuming a standing position, urination, vomiting, retching during esophagoscopy and coughing. One patient gave a history of an unknown type of trauma to his hernia prior to rupture. Although it might be expected that spontaneous rupture would be more common in patients with low serum protein, the reported serum proteins in the 21 patients varied widely. Several patients had normal or only slightly decreased values for total serum protein and/or albumin.

It is of interest that, even with massive loss of ascitic fluid through an umbilical rupture, the cardiovascular status as reflected by the blood pressure and pulse frequently remained stable. Only Flood[5] noted significant change in the vital signs immediately following rupture. On the other hand, Tracy and co-workers[11] reported the acute loss of 27 liters of ascitic fluid with maintenance of normal cardiovascular status. Five of the nine cases in which fluid loss was reported to be 5 liters or more survived this immediate catastrophic event. It should be noted that many patients who survived rupture of their umbilical hernia and its immediate sequels succumbed to other complications of chronic liver disease (hepatic coma, bleeding esophageal varices, infection, hepatorenal syndrome, etc.) months later. These deaths were probably the result of long-standing chronic liver disease rather than a sequel of umbilical hernia rupture.

Of the 21 cases of ruptured umbilical hernia, there were nine (43%) who died within 30 days. A review of these cases reveals several factors that seem to affect the immedite prognosis. The early development of such complications as hypotension, renal failure, gastrointestinal hemorrhage and hepatic coma was inevitably associated with early death. Of the seven patients who developed peritonitis, there were only two survivors. Eight patients were reported who had none of the above complications following umbilical hernia rupture. All of these patients survived

There was a correlation found between the serum albumin levels and immediate survival. Twelve cases reported serum albumin levels. Eight of these patients had a serum albumin value above 2.4 gm./dl. and survived. Four patients who had lower values of serum albumin died. When the total serum protein was considered, six of the seven (86%) with values above 5.8 gm./dl. survived and only two of the six (33%) with values below that level survived. The level of serum albumin seemed to be a better prognostic measure than the level of total protein. It must be kept in mind, however, that those patients with low serum albumins probably had more severe liver disease and thus were less able to tolerate an acute catastrophic episode such as umbilical hernia rupture.

The management of patients with ruptured umbilical hernias and chronic liver disease may well have prognostic importance. Although the number of cases is small, certain conclusions seem justified. Prompt surgical treatment is essential. The seven patients who did not receive surgery died within 30 days after rupture of the umbilicus. Of the 12 patients who had umbilical hernia repair, there were 10 (83%) long-term survivors. In addition to surgical repair, these patients also received appropriate fluid and electrolyte replacement, antibiotics and measures to decrease intra-abdominal pressure such as low sodium diet, diuretics and paracenteses.

It is of interest to note that two patients were treated with a portacaval shunt and both survived. No conclusions can be drawn about the role of portacaval shunting on the basis of only two cases. Baron[7] suggested that this operation was of value since umbilical herniorrhaphy alone removes important portacaval collaterals at the umbilical area and may result in increased portal pressure with resultant bleeding from esophageal varices. Our third case was treated with immediate umbilical herniorrhaphy. Although the patient tolerated the procedure well, there was evidence of increasing portal hypertension marked by rapid accumulation of ascites and rupture of large esophageal and gastric varices. This patient supports Baron's contention that umbilical herniorrhaphy alone results in a significant increase in portal pressure.

As with many serious medical conditions, the importance of prophylactic treatment to prevent rupture of an umbilical hernia in patients with ascites is important. The patient with chronic liver disease and ascites should be treated appropriately with sodium restriction and diuretics to prevent the accumulation of massive ascites. The development of an umbilical hernia in the presence of ascites should alert the clinician to a potentially dangerous condition. Consideration should be given to early surgical repair of such a hernia while it is small in spite of the presence of some ascites. It has been traditional to delay such repair until the ascites has been eliminated. Perhaps this concept needs to be re-evaluated. Patients with ascites and an umbilical hernia should be cautioned to avoid maneuvers which increase intra-abdominal pressure. It may be beneficial for such patients to wear a protective dressing or shield over their umbilicus as well as a firm support to prevent protrusion of the hernia. The presence of discoloration, ulceration, or the rapid increase in size of the hernia are danger signals. A patient with these signs should be immediately hospitalized for the rapid reduction of intra-abdominal pressure by paracentesis or vigorous diuresis with appropriate monitoring for the appearance of hepatic encephalopathy. The dangers of allowing the continuance of a high intra-abdominal pressure in a patient with a discolored umbilicus outweigh the danger of inducing hepatic encephalopathy by paracentesis or vigorous diuresis in a hospital setting. If the clinician is aware of the potential of umbilical hernia rupture in his ascitic patient and takes measures to prevent it, this complication may become a rarity.

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Communication from Abroad

Malabsorption in Giardiasis

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Twenty-five adult patients with giardiasis (20 males and five females) in various age groups were studied. The patients had varying severity of infestation but all of them were symptomatic.

Examination of stool samples and duodenal aspirate was carried out in each case and a study was made to substantiate malabsorption, if present, by carrying out absorption studies for carbohydrates (d-xylose test) fats (fat balance studies) and proteins (proline test). Jejunal biopsy and barium studies of small intestines were carried out.

Ten healthy control subjects of comparable age and sex were also studied. The noteworthy observations were severity of infestation as judged from stool. Examination had no relationship to alteration in absorption studies.

D-xylose was found to be abnormal in only 4% of the cases while fecal fat was abnormal in 12% of the cases. In one patient marked steatorrhea (22 gm./day) was noticed which responded to eradication of the parasite. Proline test was normal in all patients, except one who suffered from idiopathic tropical sprue. It was concluded that *Giardia lamblia* does not manifest as protein malabsorption.

Radiological examination did not reveal any significant duodenal pathology but jejunal mucosal hypertrophy was present in 40% of patients as opposed to 20% in normal controls. A definite pattern suggestive of malabsorption could be detected only in one case who had tropical sprue.

None of our patients had nodular lymphoid hyperplasia on radiological examination. Jejunal biopsy had abnormal dissecting microscopic appearances in eight patients and revealed histological abnormality in two of them. A correlation of abnormality on dissecting microscopic examination and histological sectioning was lacking.

No mucosal invasion by the parasite was recorded in the jejunal biopsy specimen. It is therefore concluded that infestation with *Giardia lamblia* had

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little effect upon jejunal absorption studies despite the finding of jejunal mucosal hypertrophy and histopathological abnormal changes in the mucosal structure in approximately an equal number of cases.

Frank malabsorption syndrome does not occur in giardiasis and when present is indicative of a co-existing disease which should be looked for.

Giardiasis is of worldwide prevalence. It may remain an asymptomatic casual inhabitant of the upper part of the small intestine or cause symptoms of diarrhea, weight loss, flatulence and colic.

The role of *Giardia* in causing chronic intestinal malabsorption is controversial. Studies in children suffering from giardiasis tend to show that malabsorption can be caused by the parasite.[1, 2, 3] On the contrary, studies in adults have been controversial. They have been either on single case reports or the work has been done in a highly selected limited number of cases[4, 5, 6] Tewari and Tandon[7] studied 30 adults with giardiasis and found unequivocal evidence of steatorrhea in half of their patients. Similarly Hoskins, et al[8] found carbohydrate malabsorption more prevalent than steatorrhea in giardiasis. In contrast to the above Palumbo, et al,[9] after reviewing 430 cases of giardiasis at the Mayo Clinic, concluded that there was no evidence that *Giardia lamblia* gave rise to malabsorption syndrome. The conclusions of others are similar based upon their studies of a relatively small number of cases[10, 11]

Interestingly there is the reported susceptibility of patients with secretory Ig-A deficiency to symptomatic giardiasis and giardiasis may be solely responsible for diarrheal disease.[12] The present study was undertaken despite conflicting reports about the pathogenesis of giardiasis vis-à-vis malabsorption.

MATERIAL AND METHODS

The present study comprised 25 adults belonging to various age groups and of both sexes who were symptomatic in terms of some abdominal complaints and had either cysts or trophozoites of *Giardia lamblia* in their stools. The duration as well as the severity of the disease was not taken into consideration in selecting the cases so that the severity of the infestation as well as the duration of disease was variable.

Ten individuals of matched sex and age without any gastrointestinal disorders served as normal controls.

Asymptomatic carriers of *Giardia* or cases with a history of other parasitic infestations were excluded. Those patients who suffered from a known etiological disorder causing malabsorption were excluded.

In every case, in addition to a detailed clinical history and physical examination the following investigations were carried out: 1. Hemoglobin estimations. All cases with significant anemia (Hb. below 9 gm.%) were excluded. 2. Total and differential leucocyte count. 3. Erythrocyte sedimentation rate (Westergren's method). 4. Serum proteins, total proteins and differential proteins with A/G ratio. 5. Blood urea. 6. Stool examination. Fresh stool specimens were examined on three consecutive occasions in every case by direct unstained and stained with iodine as well as by the concentration and flotation methods. 7. Duodenal aspirate was done in every case in a fasting state and studied for the presence of *Giardia* cysts. 8. D-xylose test (Roe and Rice method, 1948).[13] 9. Fecal fat estimation. (Van De Kramers method, 1949)[14] 10. Proline test (Gould and Schwachman, 1956)[15]. 11. Jejunal biopsy (Watson's modification of the Crosby-Kungler capsule). The jejunal biopsy specimen was studied for dissecting microscopic appearances as well as being stained with hematoxylin and eosin stain and studied histopathologically. 12. Barium meal study of the stomach, duodenum, jejunum and ileum for duodenitis, malabsorption pattern and nodular lymphoid hyperplasia. A special reference was made concerning the mucosal pattern in the duodenum, jejunum and also in the ileum. Measurements of duodenal jejunal and ileal lumen were recorded.

The signs of malabsorption as against flocculation, segmentation and Moulage's sign were recorded in every patient.

OBSERVATIONS

Of the 25 cases there were 20 males and five females, their ages ranging from 18-48 years, average being 30.5 years.

In 23 of 24 cases there was pain in the abdomen confined to the area around the umbilicus or to the lower abdomen. Pain in the epigastric region, aggravated by meals, was present in five cases. Sixteen patients had diarrhea and the number of movements usually ranged from 5-7 per day. The stools were mostly semi-solid without any blood or mucus. They were bulky and frothy in three patients and offensive in the majority of them. The urge to defecate after eating breakfast or other meals was observed in only four of our patients.

Abdominal distention and flatulence was observed in 14 cases while a variable degree of weight loss occurred in 15 patients.

Chronic constipation was observed in 12 cases, and out of these, six cases have had bouts of diarrhea alternating with chronic constipation.

Less common symptoms included moving ball of wind (nine cases) loss of appetite (eight cases) and pain during the act of defecation (one case only).

Duration of symptoms:—The symptoms were present for a variable period ranging from a few months to over 10 years, although in 13 patients they ranged from two to five years.

Severity of Infestation:—Severity of infestation was arbitrarily divided into mild, moderate and severe, depending upon the number of cysts per high power field in the stools. The majority of patients had moderately severe infestation—14 cases—while it was mild in four cases and severe in seven cases.

Clinical examination and investigations:—Tenderness was found in one or more areas of the abdomen in 18 cases in whom it was most common in the umbilical region (10 cases) and next most common in the epigastric region (eight cases). Diffuse tenderness throughout the abdomen was present in 10 cases. The descending colon was palpable in 10 cases and the ascending colon in four cases.

By and large, anemia was not present in any of the cases, hemoglobin being more than 10 gm.%. Serum protein was higher than 6 gm.% in 18 cases while only four cases had serum protein below 6 gm.%.

The d-xylose test was abnormal only in one patient while in the other cases it was found to be within normal limits. It was the same in those patients who showed other biochemical test abnormalities suggesting malabsorption, while in the patient with the abnormal d-xylose test, no other abnormality was detected.

Fecal fat excretion was disturbed only in three patients. In one patient, it was grossly abnormal (22 gm./day) and after eradication of the parasite (as evidenced by three consecutive negative stool examinations and negative duodenal aspirate) the test was repeated after seven weeks and the repeat values tended to return towards normal (9.6 gm.%). In this patient the jejunal histology, too, was mildly abnormal.

In both other cases, fecal fat was only mildly elevated. The proline test was abnormal in only one case where the fasting values were within normal range but the level of plasma proline, after caseine feeding, was abnormally low indicating that she had protein malabsorption. In addition to this the patient had an abnormal jejunal histology and a disturbed radiological pattern although her other biochemical parameters in terms of the d-xylose test and fat balance study remained within normal range. On restudying this patient, after 16 weeks of eradication of parasite, the proline values after caseine feeding revealed minimal change and were still low.

Radiological studies did not reveal any change in the size of the duodenal bulb, duodenal and jejunal lumens as compared to normal controls. Hypertrophy of the duodenal mucosa was observed in cases of giardiasis but was also present in three normal controls. Hypertrophy of the jejunal mucosa was seen in eight cases of *giardia* and in two normal subjects; flocculation was observed in two cases and Moulage's sign was present in one case.

None of our cases revealed malformation or deformed duodenal cap, segmentation of barium in either the jejunum or the ileum or any evidence of nodular lymphoid hyperplasia. The control cases also did not show any of these abnormalities. Only one case could be said to show pattern of malabsorption. When repeat studies were done 16 weeks later, her radiological abnormalities persisted.

In those four cases in whom either d-xylose or fecal fat was disturbed, the radiological abnormalities could not be detected. In one patient where flocculation of barium was observed, the fecal fat was normal and the patient did not have any other parameters to suggest malabsorption.

Dissecting microscope appearance of jejunal biopsy revealed convoluted villi in six cases and flat mucosa in only two cases of *Giardia* while none of the control cases had such a pattern. Histology of the jejunal mucosa revealed abnormality in two cases and in one patient flattening and broadening of some of the villi was observed, in addition to infiltration of the *lamina propria* by chronic inflammatory cells. When the biopsy was repeated and studied after 16 weeks based upon the clinical improvement, the villous structure also revealed changes suggestive of its return towards normal. In the second case, shortening and blunting of the villi was seen and chronic inflammatory cells had infiltrated. The changes were considered to be mild although dissecting microscope appearances revealed flat mucosa. As both these patients had flat mucosa on dissecting microscopy it was interesting to note that the histology in the first case was grossly abnormal while in the second case it was minimally altered. This indicated that correlation of dissecting microscopy with histological pattern need not be rigidly followed.

The relationship of duration of symptoms to severity of infestation was not found in any case, both being absolutely independent of each other.

COMMENT

Despite the number of reports about the presence of a chronic malabsorption syndrome in giardiasis, the issue still remains unsettled. Of course in children it is well accepted that giardiasis can cause malabsorption which is reversible with the eradication of the parasite[3] but in adults, malabsorption has been found only in a small proportion of cases and not in all[7] although a number of reports have completely contradicted the presence of malabsorption due to giardiasis.[9, 16, 17]

The present study was undertaken mainly with a view to examining anew some of the conclusions arrived at earlier. While selecting the material we did not take into consideration either the severity of the infestation or duration of the symptomatology so that both these factors remained variable.

In two-thirds of our patients diarrhea was present and in about half of the cases chronic constipation was a predominant symptom.

A majority of the investigations carried out by us are at variance with each other and none appears to be in conformity with any other. The d-xylose was normal in all of our cases except one. This has to be considered in the light of our observation that other parameters, including fat and protein absorption studies, were undisturbed in this case. A low percentage of an abnormal d-xylose test in giardiasis in our series is in contrast to other studies where a fairly high percentage of an abnormal test has been reported.[6-8]

Fat balance study, considered to be the most reliable index of malabsorption, was disturbed in only three of our cases, grossly in one and marginally in two. In the first case, *Giardia* can be incriminated as the cause of his steatorrhea since after eradication of the parasite his fecal fat returned towards normal values after about seven weeks. This patient had an additional finding in terms of a mildly abnormal jejunal mucosa on histology although his small intestine had a normal radiological appearance. This difference is possible to understand since Laws, et al[18] have observed that the incidence and severity of flocculation bore no relationship to the fecal fat and that there was a similar lack of correlation between flocculation and jejunal biopsy. Our results of fat balance study are in conformity with those of Amini[4] and Antia, et al[19] who reported steatorrhea in three out of eight and two out of nine patients with giardiasis. Serum proline values in all of our patients, except one, were normal and that patient, too, did not reveal carbohydrate or fat malabsorption but had radiological evidence of malabsorption along with abnormal jejunal mucosal histology.

Jejunal mucosal hypertrophy was observed in 40% of our *Giardia* patients and in 20% of the control group. This observation is easy to understand since the jejunum is the main site of giardial habitat and the jejunal mucosa, which reveals flattening on histology, would reveal thickening on radiology. This explanation seemed untenable in our patients because, except in one case, all had a normal jejunal mucosa on histological examination. When a correlation of jejunal mucosal appearance on radiology and dissecting microscopy was attempted, it was seen that of eight cases, four had a leaf-like pattern, three had convoluted and one had a flat mucosa. This meant that hardly any correlation was possible and this is in accordance with the observations of Laws, et al.[18] Nodular lymphoid hyperplasia was distinct by its absence in our series.

Although jejunal biopsy smears are reported to be positive for *Giardia* in the majority of the patients[6, 20] we could not demonstrate *Giardia* in the jejunal mucosa in any of our cases. This conforms to the findings of others.[7, 21, 22] Keeping the above observations in mind, it would be very difficult to lay down any test to be the best determining index of malabsorption.

Since malabsorption could occur in relation to carbohydrates, fats, proteins, vitamins and minerals, obviously different parameters will be needed to work the malabsorption of various nutrients. Further Floch, et al[23] had observed that in untreated patients, where biopsy specimens and absorption tests were particularly abnormal, radiology of the small bowel was most abnormal. In treated patients, where the biopsy and absorption tests where only minimally abnormal, the roentgen series was only slightly abnormal. This is rather at variance with the experience of Laws, et al[18] who found that in idiopathic steatorrhea it was possible for a normal radiological appearance to be consistent with either partial or subtotal jejunal atrophy.

In view of the conflicting statements available one can only say that when a clinical suspicion of malabsorption is fairly high, abnormality of any one parameter will be indicative of malabsorption of a particular nutrient such as carbohydrate, fat, protein, etc. When, however, the jejunal mucosal abnormalities or radiological appearances are suggestive, these should be more reliable. Furthermore the greater the number of positive tests, the greater will be the confidence to label the patient as having malabsorption.

The question arises as to how *Giardia* is capable of producing malabsorption. The possible factors which have been incriminated for the causation include: 1. presence of a large number of parasites on the mucosal surface of the intestines so that the absorptive surface is considerably reduced; 2. increased motility of the gut so that the time of exposure of nutrients to the absorptive surface is reduced; 3. bacterial overgrowth; 4. invasion of the pancreatic duct; 5. injury, to the mucosa possibly by the mucosal invasion and 6. a barrier provided by the parasite to the active transport of various nutrients as demonstrated experimentally by Anand.[24] From our study, at least one of these factors of mucosal invasion seems unlikely since we could not demonstrate any parasite in the mucosa.

In the present study only two patients could satisfy the criteria of malabsorption. One patient who had biopsy changes, radiological suggestion and an abnormal proline test, clinically fitted in idiopathic tropical sprue since therapy and eradication of *Giardia* did not improve her while specific therapy for tropical sprue benefited her. Apparently *Giardia* was a coincidental finding. The second patient had marked steatorrhea and jejunal mucosal changes which responded to eradication of the parasite. Two more patients had mild steatorrhea due to giardiasis. Thus of three patients one had a picture suggestive of malabsorption while two others had only steatorrhea.

Thus, we can conclude from the present study that although *Giardia* is capable of causing steatorrhea in adults, it produces malabsorption in an insignificant number of cases. This is in contrast to the observations of Antia, et al[19] who found a disturbance of one or more parameters of absorption in eight of nine cases and Tewari and Tandon[7] who detected steatorrhea in 14 out of 30 cases studied by them.

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Clinical Vignette

Intestinal Obstruction Due to a Wandering Spleen

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A 23-year old man underwent surgery in 1967 for volvulus of the sigmoid colon. He was re-operated upon five years later for intestinal obstruction. At laparotomy, a volvulus of the sigmoid colon was again found. In addition, there was obstruction of the ascending colon due to its compression by the long pedicle of a wandering spleen, located in the right abdominal cavity. The radiological findings are described.

We present the hypothesis that a single developmental anomaly can explain both the wandering spleen and excessively mobile colon found in this patient.

Torsion or volvulus of a wandering spleen is an uncommon condition. Maingot[1] discussed approximately 175 cases in his book. The total of reported cases in the literature numbers about 350. Most instances have been found in women during the childbearing period,[2] however, cases have also been described in men and children.[3]

The wandering spleen may be found anywhere in the abdominal cavity but it is usually located in the middle abdomen or pelvis. Clinical presentation varies. There may be a chronic course manifested by mild abdominal pain and/or palpable mass often with noticed border. An acute picture due to splenic torsion or, more rarely, intestinal obstruction, is also possible.[2]

The pathogenesis of this condition is controversial. Both congenital[3, 5] and acquired[2, 4] etiologies are discussed.

We wish to report a rare case of intestinal obstruction due to the long pedicle of a wandering spleen, coexisting with volvulus of the sigmoid colon. The authors propose that this combination represents a congenital rather than an acquired pathogenesis.

CASE REPORT

A 25-year old, mentally retarded, Jewish male, was hospitalized in July, 1972, because of acute intestinal obstruction. In December, 1967, the patient was hospitalized elsewhere because of an "acute abdomen". Laparotomy revealed a volvulus of the sigmoid colon accompanied by dilatation of the large bowel. Because of severe ischemic changes of the involved bowel, partial sigmoidectomy was performed. The patient was asymptomatic until July, 1972, when he was hospitalized following a two-month history of increasing abdominal pain, constipation, nausea and vomiting.

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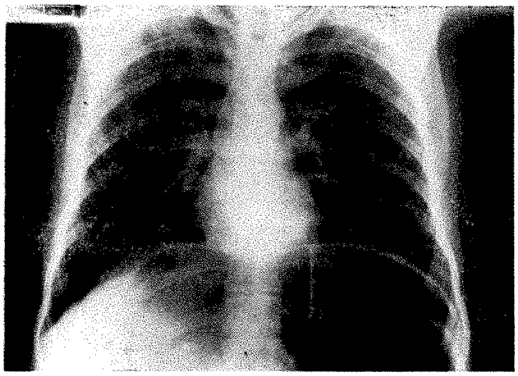

Fig. 1—Chest film reveals normal heart and lungs. Dilatation of the colon is noted on the left.

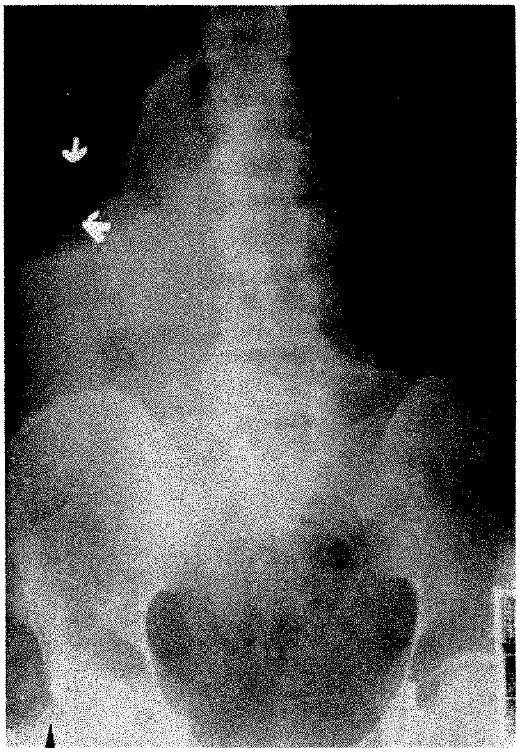

Fig. 2—Marked dilatation of the colon from the sigmoid to the hepatic flexure with absence of air in the region of the cecum and rectum.
No splenic shadow is seen on the left. Arrows denote location of splenic shadow in the right abdomen.

On admission the patient's general condition was good. Blood pressure was 130/80 mm. Hg.; temperature 37.4 C. The abdomen was distended, with diffuse tenderness on palpation. A somewhat round mass with a diameter of 12 cm. was palpated in the right upper abdomen. The rest of the physical examination was unremarkable.

Laboratory investigations included: hemoglobin, 11.2 gm./100 ml.; WBC, 7 000 cu. mm. with a normal differential. Urinalysis, BUN and blood glucose were within normal limits. On radiological examination, the chest film (Fig. 1) disclosed a normal heart and lungs. Dilatation of the colon, particularly on the left side, was noted. Plain abdominal films (Fig. 2) demonstrated marked dilatation of the colon from the sigmoid to the hepatic flexure. No air was present in the area normally occupied by the rectum and cecum. The splenic shadow was not detected in its normal location. These films suggested intestinal obstruction at the level of the sigmoid colon and a second obstruction at the level of the ascending colon. In retrospect, the shadow observed in the right abdomen can be attributed to the spleen. Barium enema (Fig. 3), showed a typical picture of volvulus of the sigmoid colon with significant proximal dilatation of the colon.

Laparotomy revealed a volvulus of the sigmoid and a markedly dilatated colon. The volvulus was reduced and excessive colonic air emptied through a rectal tube. A fibrous band, containing blood vessels, crossed the abdomen from the left upper quadrant to the right flank. This band compressed the ascending colon. The spleen was located near the cecum and was removed, together with its fibrous pedicle, thereby relieving the compression on the ascending colon.

The spleen measured 8 × 15 × 16 cm. The hilum was 5 cm. in diameter and con-

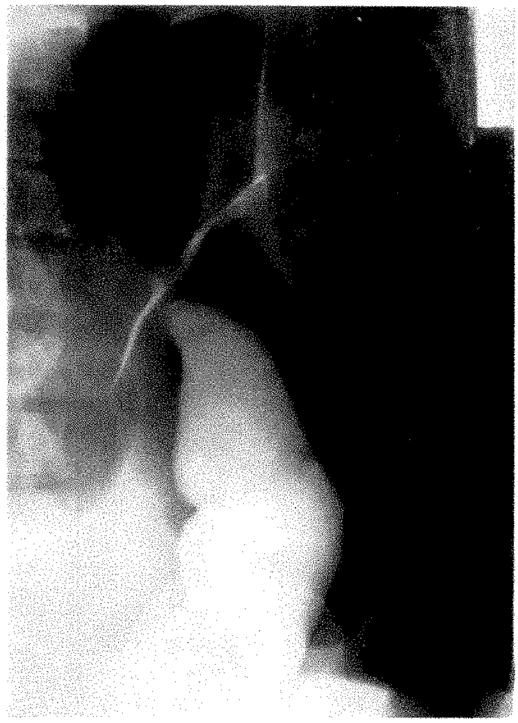

Fig. 3—Portion of barium enema shows volvulus of the sigmoid and proximal dilatation of the colon.

tained a congenital vascular malformation. The splenic sinusoids were enlarged and congested, probably due to obstruction of the venous circulation. The postoperative course was unremarkable. The patient felt well until August, 1976, when he was reoperated upon elsewhere for recurrent volvulus of the sigmoid colon.

COMMENT

Intestinal obstruction due to a wandering spleen is quite rare. Abell's[1] review of 97 cases of wandering spleen contained only seven instances of intestinal obstruction attributed to splenic adherence or compression.

The pathogenesis of torsion of the wandering spleen has been explained on the basis of either acquired factors, congenital factors or a combination of both.[4] In Abell's series[2] most patients were between the ages of 10 and 40. Five and two tenths per cent were over the age of 50 and only one episode was reported in a child younger than 10. He concluded that the occurrence of most cases of wandering spleen during adulthood favors an acquired rather than a congenital etiology.[2]

Simpson[4] also favors an acquired etiology but for different reasons. He claims that weakness of the abdominal wall, multiple pregnancies and hormonal changes associated with pregnancy are the significant factors in the pathogenesis of wandering spleen.

Other authors suggest a congenital etiology for torsion of the wandering spleen. Absence or laxity of the supporting ligaments of the spleen, or excessive length of the splenic pedicle support such an etiology.

Truesdale and Freedman[6] for example, were among those who claim that a long splenic pedicle is due to abnormal embryonic development. Woodward[5] expressed the idea that the increased mobility of the spleen may be due to incomplete fusion of the mesogastrium posteriorly. This would result in the formation of a pancreas which is not completely retroperitoneal. In one of the cases reported by Smulewicz and Clemett[7] the tail of the pancreas was in fact found to be intraperitoneal.

Carswell's[3] investigation strongly favors a congenital etiology. He described 11 cases of wandering spleen, only three of which occurred in children over the age of 10. In two of the children, a persistent mesentry of the descending colon was found. One of the cases exhibited hypermobility of the cecum and ascending colon.

The spleen as well as the colon develops from the dorsal mesogastrium; therefore, an abnormality or series of abnormalities in the development of the dorsal mesogastrium could explain the occurrence of both wandering spleen and hypermobility of the colon.

In the case presented here, a wandering spleen with a long pedicle was found displaced to the right abdominal flank, where it compressed the ascending colon. In addition, this case demonstrates marked hypermobility of the colon, manifested clinically by repeated episodes of volvulous of the sigmoid. The simultaneous occurrence of these two anomalies strongly favors a congenital etiology for torsion of the wandering spleen.

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Clinical Vignette

Aortoduodenal Fistula

ROLE OF ENDOSCOPY IN DIAGNOSIS

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A patient with an aortic by-pass graft presented with intermittent gastrointestinal bleeding. A definitive diagnosis of an aortoenteric fistula involving the third part of the duodenum was made at endoscopy. Diagnosis of an aortoenteric fistula is often difficult with angiography and barium contrast studies, frequently being negative. Since the majority of these fistulas involve the distal duodenum, early endoscopy should be considered when an aortoenteric fistula is suspected.

Aortoenteric fistula is a relatively rare but extremely important complication of abdominal aortic reconstructive procedures. These fistulas may present with hemorrhage, septic complications or both. The hemorrhage may be massive and continuous but intermittent bleeding frequently occurs. The diagnosis of such a fistula may be difficult since barium x-ray studies are frequently negative and since angiography is unrevealing during the intervals between acute bleeding.[1] In this case, the patient presented with intermittent abdominal pain and gastrointestinal bleeding. Aortography was negative. The definitive diagnosis of an aortoduodenal fistula was made by endoscopy.

CASE REPORT

A 56-year old man had resection of an abdominal aortic aneurysm with replacement by a dacron, aortofemoral bypass graft in June, 1975. Postoperatively, he remained well until May, 1977, when he presented with a three-week history of intermittent, severe, cramping abdominal pain associated with diarrhea, melena and diaphoresis. He also noted the onset of angina during this period. Physical examination revealed a pale man with postural hypotension and minimal epigastric tenderness. His hemoglobin was 6.1 gm./100 ml., stool guaiac was positive and nasogastric aspirate was guaiac negative.

After the patient was stabilized, aortography was performed because of the possibility that he was bleeding from an aortoenteric fistula. This examination revealed a normal appearing graft with no evidence of extravasation of contrast material outside of the aortic lumen. Upper gastrointestinal endoscopy was then performed with an Olympus GIF-D3 forward-viewing endoscope. The endoscopic findings included a normal esophagus, stomach and proximal duodenum. In the third portion of the duodenum a bile stained mass partially covered with blood clot was seen (Fig. 1). Closer inspection of this area revealed that the mass was formed by woven dacron fabric confirming the presence of an aortoduodenal fistula (Fig. 2). The duodenal mucosa surrounding the graft was friable and a small amount of active bleeding was noted in this area. The graft was not pulsatile.

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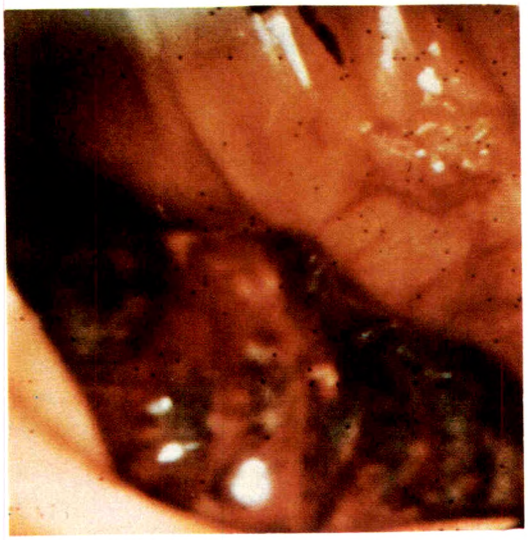

Fig. 1—Endoscopic view of the lesion in the third part of the duodenum.

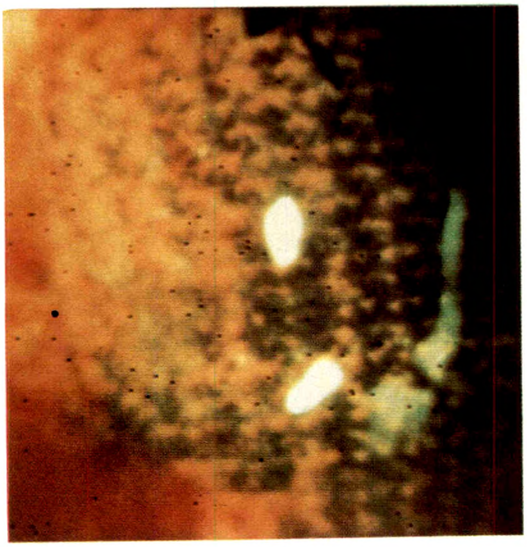

Fig. 2—A close endoscopic view of the aortic graft demonstrating the woven dacron fabric.

Based on the endoscopic findings, the patient had a two-stage surgical procedure consisting initially of bilateral axillofemoral by-pass grafts, followed in four days by resection of an infected aortofemoral by-pass graft and closure of the duodenal defect (Fig. 3). Cultures taken from the graft subsequently grew *Klebsiella pneumoniae* and *Enterobacter hafniae*.

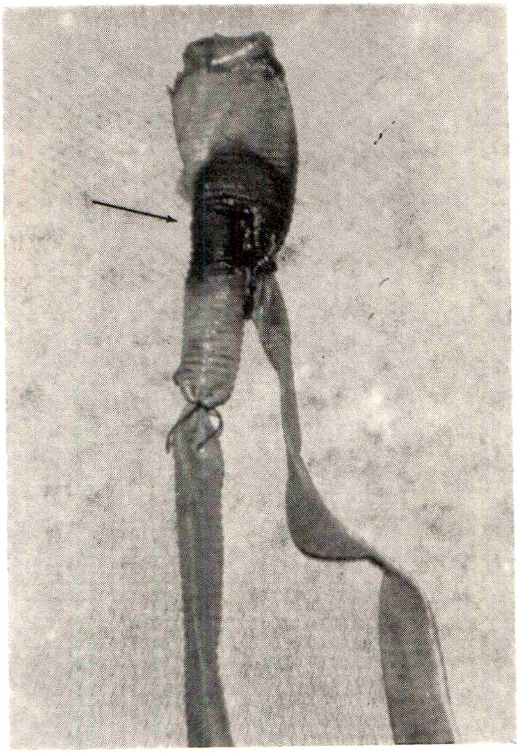

Fig. 3—The resected aortic prosthesis. Note that the area involved in the aortoduodenal fistula is bile stained (arrow).

The patient did well until 16 days postoperatively when he developed fever, leucocytosis and right flank pain. On the 17th postoperative day, he developed massive upper gastrointestinal bleeding which was localized to the third part of the duodenum by endoscopy. At emergency laparotomy, he was found to have a large infected hematoma with dehiscence of his aortic stump closure and erosion of the duodenal wall. He died during this operative procedure.

COMMENT

Fistulization between an aortic prosthesis and the intestine may result in direct communication between the vascular and intestinal lumen, or in a paraprosthetic-enteric fistula in which there is no direct communication with the vascular lumen. This case initially represented a paraprosthetic duodenal fistula with bleeding from the duodenal wall and through the interstices of the graft. Sepsis is the other major manifestation of paraprosthetic enteric fistulas and was found in 14 of 21 patients recently reviewed by O'Mara.[2] When sepsis involves the anastomosis, suture line disruption with resultant massive hemorrhage will occur.

Although a barium contrast study[3] or angiography may occasionally be diagnostic of an aortoenteric fistula, more commonly these studies are unrevealing. Failure to make the diagnosis at laparotomy has also occurred when the association between hemorrhage or sepsis with an abdominal aortic prosthesis was not considered.[1]

The endoscopic diagnosis of an aortoenteric fistula has rarely been reported. Two cases of aortoduodenal fistula [4, 5] and one case of a fistula between a renal artery graft and the duodenum[6] successfully diagnosed by endoscopy have been reported. Negative endoscopies have also been reported, however, in a case of aortoduodenal fistula.[7] The successful endoscopic diagnosis in this case resulted from a high index of suspicion coupled with careful examination of the distal duodenum.

Since the majority of aortoenteric fistulas involve the distal duodenum,[8] early endoscopy should be included in the diagnostic evaluation of patients with an aortic prosthesis who present with either gastrointestinal bleeding or septic problems. The endoscopist should be prepared to inspect the third and fourth portions of the duodenum and should be aware of the fact that the prosthesis may be bile stained. Demonstration of active bleeding in the distal duodenum is highly suggestive of an aortoduodenal fistula and visualization of the prosthesis is diagnostic. A negative endoscopy should be followed by angiography in actively bleeding patients, however, when the diagnosis is suspected, exploratory surgery should not be delayed because of negative diagnostic studies.

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Clinical Vignette

Vagotogenic Cholecystitis

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Truncal vagotomy provokes acute cholecystitis in the stone-containing gallbladder of dogs. An apparently similar sequence has been fortuitously observed in three patients. These circumstances suggest that where cholelithiasis is encountered in a clinical situation in which truncal vagotomy is performed, cholecystectomy or stone removal and cholecystostomy be done as a synchronous adjunctive procedure.

Three chance experiences with patients appear to provide a clinical parallel to an experimental observation in dogs.

Experiments by Schein, et al[1] have demonstrated the influence of vagotomy on the calculus-containing gallbladder. One washed human cholesterol gallstone had been inserted into the gallbladder of each of 12 dogs. Six of the dogs then underwent bilateral infradiaphragmatic vagotomy. The other six served as controls. A laparotomy was performed six to eight weeks later.

There was no unusual reaction in the control animals who had had a stone inserted. There was a striking change in five of the six dogs which had also been vagotomized. They exhibited acute cholecystitis manifested by edema and marked congestion. One of the animals had a small localized pericholecystic abscess. The histologic changes were characteristic of acute cholecystitis.

CLINICAL MATERIAL

Case 1:—A 57-year old man was admitted for massive upper intestinal bleeding. He had been treated for rheumatoid arthritis with gold and aspirin. A gastrectomy and truncal vagotomy were performed for erosive gastritis. The bleeding did not recur but the postoperative course was complicated by a wound infection and pulmonary complications requiring tracheotomy.

Four weeks later the patient complained of abdominal pain and a tender enlarged gallbladder was palpated. On the 31st postoperative day a second operation was undertaken for acute gangrenous cholecystitis. A cholecystostomy was performed and multiple calculi were extracted. The patient died of multiple system failure on the tenth postoperative day.

Case 2:—An 81-year old debilitated chronically ill lady was admitted for upper gastrointestinal bleeding. Six units of blood were replaced before surgery was performed for a bleeding duodenal ulcer. A pyloroplasty and truncal vagotomy effectively controlled the bleeding. A stone-filled gallbladder was noted; it was the surgeon's judgment that the risk of an additional procedure was not warranted. Eighty-two days later a second operation was required for gangrenous perforated cholecystitis.

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Cholecystostomy and cholecystolithotomy tided the patient over this episode. She was returned to the nursing facility with a clamped-off indwelling cholecystostomy tube left in as a vent.

Case 3:—A 76-year old lady was treated for a bleeding duodenal ulcer by suture ligation of the bleeding vessel, pyloroplasty and bilateral vagotomy. A large solitary gallstone was noted. In the third postoperative week she complained of abdominal pain and fever. A large tender gallbladder was easily palpated. At the second operation there was an acute perforated cholecystitis. A cholecystectomy was performed. The postoperative course was uneventful.

Each patient had innocuous cholelithiasis at the initial operation. After truncal vagotomy each presented with advanced acute cholecystitis.

COMMENT

There are parallels in this clinical and experimental situation. In each instance (except for one dog) after truncal vagotomy the innocuous stone containing gallbladder became the site of an acute cholecystitis.

The mechanism by which this occurs is not clear. In the experimental situation there was no cystic duct obstruction. In the clinical situation this was not clearly ascertained. Further, vagotomy decreases the pressure needed to evacuate bile from the gallbladder through the cystic duct into the duodenum by a range of 28-62% with an average of 42%.[2]

Vagotomy, however, paralyzes the contractile musculature of the gallbladder. Emptying is impaired. The contents of such neurogenic gallbladders becomes static. Stasis plus calculi can produce acute cholecystitis in dogs and this is presently assumed to be the mechanism in these patients. This has been described by Johnson and Boyden[3] and Morris, et al.[4] Therefore it is assumed that the loss of motor power is more significant than the reduction of pressure across the cystic duct choledochal junction.

In the dogs the acute cholecystitis was noted 42-56 days after the experimental situation was established. In patients it appeared at 20, 35, and 82 days postvagotomy—an average of 45.7 days.

In the dog experiments a solitary stone was implanted. In the patients one had a solitary cholesterol stone and the two others had multiple calculi.

Some of the reports of acute cholecystitis appearing after gastrectomy with high ligation of the left gastric artery may be assumed to be, at least in part, due to the disruption of the hepatic plexus fibers.[5, 6]

This vagotogenic circumstance is apart from that variety of acute cholecystitis encountered after an unrelated (even extra-abdominal) operation. In that entity described by Glenn and Wantz[7] the gallbladder is often acalculus and the etiologic factors are presumed to be starvation stasis and the local hypertensive state induced by narcotics.

The provocation of acute cholecystitis in the stone-containing gallbladder by vagotomy occurs in both dog and man. The recognition of the relationship has led us to do a cholecystectomy or cholecystolithotomy or cholecystostomy for the stone-containing gallbladder in the individual who is having a truncal vagotomy. With this policy the problem of vagotogenic provoked cholecystitis can be eliminated.

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The Radiology Corner*

DUODENOCOLONIC FISTULA WITH GALLSTONE ILEUS

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Biliary enteric fistula is one of the complications of cholelithiasis, occurring in about 3-5% of all patients with gallstones. By far the most common type of fistula is the cholecystoduodenal, occurring in over 60 percent of the cases.[1] Cholecystocolic, choledochoduodenal, and cholecystogastric follow in decreasing order of frequency.[1] The gallstone ileus syndrome occurs less than one-tenth as frequently as biliary enteric fistula because most of the stones pass harmlessly through the gastrointestinal tract.[1] We recently encountered a patient with a cholecystoduodenocolonic fistula and gallstone ileus. This combination has only been reported in four previous patients.[3, 4]

CASE REPORT

E. R., an 81-year old caucasian female presented in the emergency room because of a three-day history of nausea, vomiting and flu-like symptoms. Prior to this, she had been in excellent health. She denied jaundice, fatty food intolerance, dark urine or light colored stools. She had had no operations.

Physical examination revealed an obese female appearing acutely ill. There was no jaundice.

Abdominal examination showed the presence of bowel sounds and minimal upper abdominal tenderness without guarding or rebound tenderness. The remainder of the physical examination was within normal limits.

Laboratory studies included normal liver function studies; BUN of 49 mg./dl., Hgb., 13.8 gm./dl.; Hct., 38.1% and WBC, 17,000 with a shift to the left.

An upper gastrointestinal series was performed and demonstrated a duodenocolic fistula and a smooth mass obstructing the fourth portion of the duodenum (Fig. 1). There was no air in the biliary tree. Barium enema also demonstrated the duodenocolic fistula and showed no evidence of neoplasm (Fig. 2). An intravenous cholangiogram showed a normal common bile duct without filling of the gallbladder.

The patient developed profound hyponatremia with a serum sodium concentration of 121 mEq./l. After correction of the electrolyte abnormalities, laparotomy was performed. A large gallstone was found and removed from the jejunum (Fig. 3). The presence of cholecystitis with a cholecystoduodenocolic fistula was confirmed. There was no abscess formation. Primary closure of the colonic and duodenal perforations was carried out followed by cholecystectomy. An operative cholangiogram was normal.

The patient's postoperative course was free of complications and she was dis-

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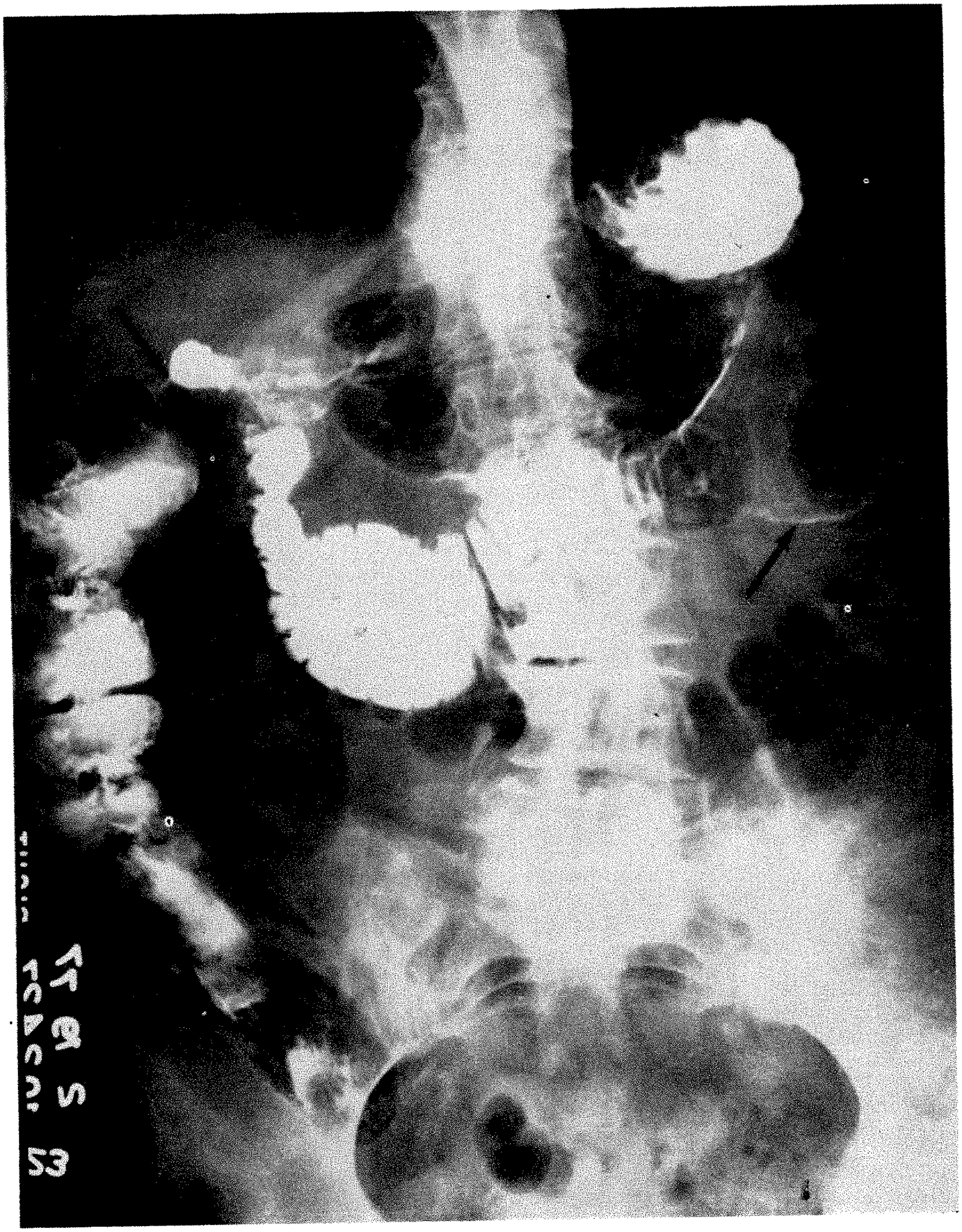

Fig. 1—Supine film of an upper gastrointestinal examination with barium, showing a duodenocolic fistula (right arrow) and a smooth mass obstructing the fourth portion of the duodenum (left arrow). Barium entered the right colon via the duodenocolic fistula.

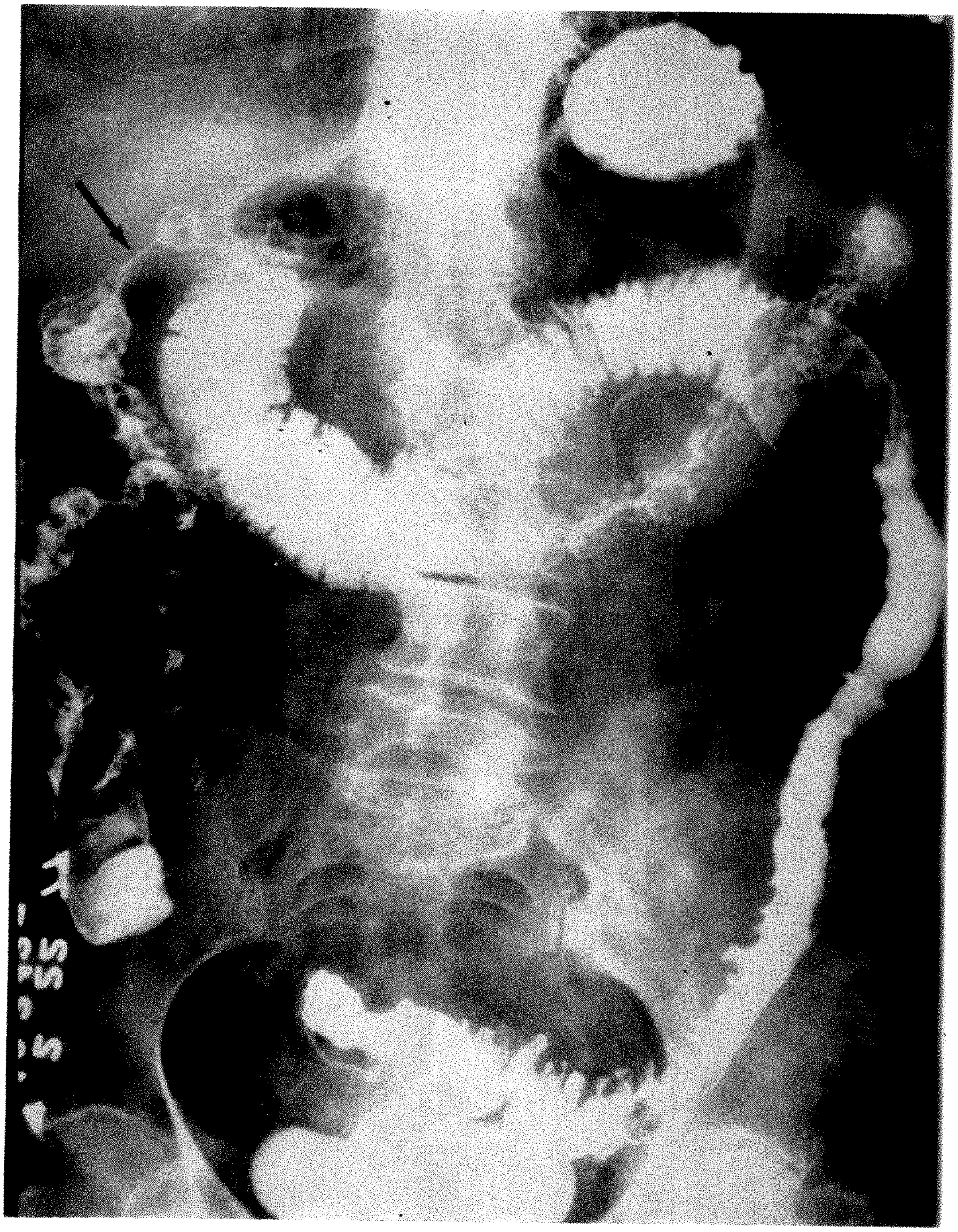

Fig. 2—Postevacuation film of a barium enema, performed three days following the upper gastrointestinal examination. The duodenocolic fistula is again demonstrated, with barium from the colon filling the duodenum and stomach. The right arrow points to the fistula. The left arrow points to the large filling defect seen immediately past the duodenal jejunal junction.

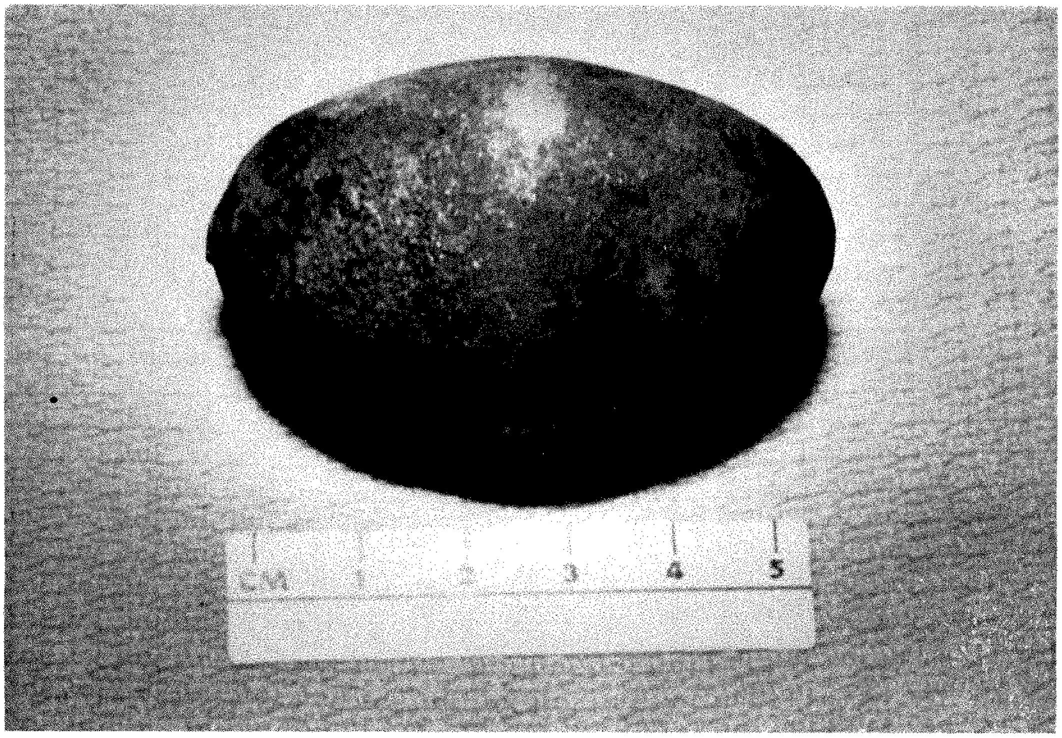

Fig. 3—Photograph of a large gallstone removed at laparotomy from the jejunum. It measured more than 5 cm. in greatest diameter.

charged on the ninth postoperative day. She remains asymptomatic at the present time (three months later).

COMMENT

The diagnostic radiographic findings of biliary enteric fistula with gallstone ileus are: 1. air in the biliary tree; 2. mechanical small bowel obstruction; 3. presence of a calcified gallstone in the abdomen.

A requirement for pneumobilia is either a patent cystic duct or a fistula involving the common bile duct. In the majority of patients, cystic duct obstruction is the pathophysiologic event which causes acute cholecystitis and eventually leads to biliary enteric fistula; therefore, cystic duct obstruction is a common finding, especially if the process is acute. For this reason, it is not unusual for this finding (air in the biliary tree) to be absent. Air in the biliary tree, absent in our patient, is not found in 25-50% of reported cases.

Gallstone ileus accounts for only 1-2% of mechanical obstructions of the small intestine. In patients more than 65 years of age, the incidence rises to about 20-24%.

In our patient, the problems usually associated with a high mechanical small bowel obstruction were somewhat lessened because of internal decompression of the obstruction by the duodenocolic fistula. The most frequent level of obstruction by the gallstone is the distal ileum. The ligament of Treitz is a less frequent level of obstruction and even more rarely, other levels of the small intestine can be the site of obstruction. The level of obstruction in our patient was approximately 10 cm. distal to the ligament of Treitz in the proximal jejunum.

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The Last Page

QUESTIONS IN GASTROENTEROLOGY

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The Last Page appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. INDICATIONS FOR PERITONEOSCOPY INCLUDE:

A. Diagnosis of jaundice and ascites.

B. Inconclusive liver scans.

C. Ill-defined abdominal masses.

D. Staging for Hodgkin's disease.

(Page 642)

2. FEATURES SUGGESTIVE OF CROHN'S DISEASE OF THE ESOPHAGUS ARE:

A. Transmural inflammation.

B. Muscular hypertrophy.

C. Neuromatous lesions with hypertrophied nerves.

D. Areas of granuloma formation.

(Page 651)

3. EVALUATIONS OF CARDIOVASCULAR RESPONSES TO UPPER GASTROINTESTINAL ENDOSCOPY REVEAL:

A. Well-documented prospective evidence to implicate vagovagal reflexes as a causal agent.

B. That the rise in rate pressure product indicates that endoscopy represents a mild but significant form of cardiac stress.

C. Mean increases of work pressure products of 33% occur with endoscopy compared to 200-300% increase in cardiac stress testing.

D. That prophylactic atropine should be given.

(Page 660)

4. ALPHA-ADRENERGIC BLOCKING AGENTS SUCH AS DIHYDROERGOTAMINE OR PHENTOLAMINE:

A. Potentiate cholecystokinin- (CCK) induced gallbladder emptying.

B. Potentiate the effects of relaxation mediating beta-receptors on the gallbladder and sphincter of Oddi.

C. Induce duodenal spasticity due to cholinergic hyperactivity.

D. Stimulate gastric emptying.

(Page 666)

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5. PANCREATIC ABSCESS:

A. Usually occurs after pancreatitis due to alcoholic or biliary tract disease.

B. Develops rapidly in one or two days after the initial attack on pancreatitis.

C. Is only rarely associated with obstructive jaundice.

D. May be diagnosed by a skinny needle transhepatic cholangiogram.

(Page 671)

6. USE OF 5, 5-DIMETHYL-2, 4—OXAZOLIDINEDIONE (DMO) TO EVALUATE PANCREATIC FUNCTION HAS SHOWN THAT:

A. There is a decrease in pancreatic DMO excretion in the early stages of chronic pancreatitis when bicarbonate concentration and volume are still normal.

B. An intraductal outflow barrier is initially responsible for impaired excretion but as the chronic pancreatitis progresses an extraductal diffusion barrier develops as well.

C. DMO is produced by metabolic N-demethylation of oral Trimethadione.

D. The DMO test has a diagnostic accuracy of 50%, and is superior to the 40% diagnostic accuracy seen with the pancreozymin-secretin test.

(Page 680)

7. CONCERNING ETHIOINE INDUCED PANCREATITIS:

A. Ethionine exerts its toxic effects upon the pancreatic acinar cell after zymogen synthesis has occurred.

B. The addition of methionine to the diet will prevent the pancreatitis.

C. Pretreatment with Beta-3-thienylalanine (β-3TA), an inhibitor of zymogen formation, will prevent this drug induced pancreatitis.

D. Phenylalanine in the diet will block the effect of β-3TA.

(Page 685)

8. CONCERNING UMBILICAL HERNIAS IN PATIENTS WITH ASCITES:

A. Umbilical herniorrhaphy alone by removing portacaval collaterals at the umbilical area may result in increased portal pressure with resultant bleeding from esophageal varices.

B. If the hernia is discolored, ulcerated or rapidly increasing in size the patient should be immediately hospitalized for rapid reduction of intra-abdominal pressure.

C. If the hernia ruptures, patients with higher levels of serum albumin have a better chance of survival.

D. When the hernia ruptures the patient should be treated conservatively as surgical treatment has an almost 100% mortality.

(Page 691)

9. GIARDIASIS:

A. Causes malabsorption in adults in only a small proportion of cases.

B. Although producing clinically significant illness, may be associated with a normal jejunal biopsy.

C. Is usually associated with an abnormal d-xylose test.

D. Produces a microcytic-hypochromic anemia.

(Pages 697 and 698)

10. A WANDERING SPLEEN:

A. Can undergo torsion or volvulus.

B. Is usually found in the middle abdomen or pelvis.

C. Commonly has its clinical presentation in children under the age of ten.

D. May be associated with hypermotility of the colon.

(Page 703)

11. CONCERNING AORTIC BY-PASS GRAFTING AND FISTULA FORMATION:

A. A paraprosthetic enteric fistula may present as sepsis or gastrointestinal bleeding.

B. The majority of aortoenteric fistulas involve the mid jejunum.

C. These fistulas can easily be diagnosed by appropriate barium contrast and angiographic studies.

D. Endoscopy of the third and fourth portions of the duodenum may reveal active bleeding or visualization of the prosthesis.

(Page 707)

12. TRUNCAL VAGOTOMY:

A. Causes an increased incidence of cholecystitis in the acalculus gallbladder.

B. Paralyzes the contractile musculature of the gallbladder.

C. Increases the pressure needed to evacuate bile from the gallbladder through the cystic duct into the duodenum.

D. May provoke acute cholecystitis in the stone containing gallbladder.

(Page 709)

13. CONCERNING THE BILIARY ENTERIC FISTULA:

A. The most common type is the choledochoduodenal occurring in over 60% of cases.

B. Air in the biliary tract is present in 90% of reported cases.

C. This complication occurs in less than 1% of all patients with gallstones.

D. The gallstone ileus syndrome occurs less than one-tenth as frequently as biliary enteric fistula.

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

Genetics of Human Cancer—Progress in Cancer Research and Therapy, Vol. 3: edited by John J. Mulvihill, M.D., Robert W. Miller, M.D. and Joseph F. Fraumeni, Jr., M.D. 519 pages, illustrated. Raven Press, New York, NY 1977.

Genetics of Human Cancer is a multi-authored text of some 46 chapters grouped as follows: Population Genetics, Birth Defects and Cancer, Cancer Cytogenetics, Cancer in Single Gene Disorders, Familial Cancer, Genetic Markers, Cellular Biology, Genetic Theories of Pathogenesis, etc. This is a well written, well edited tome which should be read by those interested in oncology.

David A. Dreiling, M.D., F.A.C.G.

Intestinal Ischaemia: by Adrian Marston, 190 pages, illustrated. Year Book Medical Publishers, Chicago, IL, 1977. Price $20.00.

This monograph is an excellent summary of our present knowledge on intestinal ischemia. It contains a wealth of information on the mesenteric macro- and microcirculations and the circumstances of circulatory failure.

The chapter on regulation of intestinal blood flow and the technics employed in blood flow studies is quite informative and very precisely written and illustrated.

The chapter on acute intestinal failure and on intestinal angina are well structured and should be of interest to the surgeon and gastroenterologist.

Finally, the section of ischemic colitis summarizes new information on this syndrome, which the author has brought to our attention through many previous publications.

This monograph will gain quick and wide recognition among clinicians and investigators interested in the field of gastroenterology in general and intestinal circulation in particular.

Demetrius Pertsemlidis, M.D., F.A.C.G.

Surgery Annual—1977: edited by Lloyd M. Nyhus, M.D., F.A.C.G. (Hon.) 427 pages, illustrated. Appleton-Century-Crofts, New York, NY, 1977. Price $26.50.

This book is essentially an update in progress made in crucial areas of surgery. The list of contributors includes many prominent surgeons known internationally for their contributions to advancement in the field of their treatise.

The book is highly recommended to all surgeons.

Demetrius Pertsemlidis, M.D., F.A.C.G.

Liver, Bile Ducts, and Pancreas: by T. T. White, M.D., H. Sarles, M.D. and J-P Benhamou, M.D. 440 pages, illustrated. Grune & Stratton, New York, NY, 1977. Price $32.50.

Liver, Bile Ducts and Pancreas is a splendid monograph re-edited and re-written from a text originally published in French. The authors and their collaborators represent, in my opinion, the outstanding authorities of their field and the manuscript does them credit. The trust is towards clarity and simplicity making the book invaluable for the medical student, resident, general practitioner and nongastroenterologist. I strongly recommend it to these groups.

David A. Dreiling, M.D., F.A.C.G.

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Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.

Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
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DOSAGE AND ADMINISTRATION: CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
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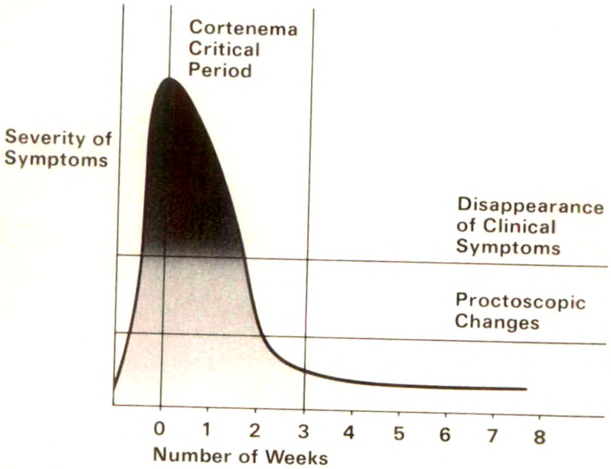

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